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FOREWORD

The title of this publication "THE JOURNAL OF UROLOGY, experimental, medical and surgical" expresses briefly the aims, hopes and ambitions of the editors.

Recent years have been very prolific in the production of splendid papers on the urinary tract, its adnexa, and correlated subjects. Many of those from the departments of physiology, pharmacology, chemistry, pathology and bacteriology have been scattered through the various special journals on those subjects. The embryological and anatomical researches have likewise appeared in journals devoted to those fields. Medical articles on the kidney, adrenals, urine, etc., and the many diseases which are secondary or correlated, and surgical papers of a similar scope, have found lodgement in dozens of diversified journals all over the country.

The situation is such that one who is interested in all forms of research in this field, anxious to keep abreast with what the internists are doing along these lines and at the same time desirous of following the progress of surgical urology, is overwhelmed with the magnitude of the task, and overlooks or fails to discover much that is important. The medical and surgical urologists have much in common, both are dependent on the progress made in experimental researches, and all concerned could be greatly broadened by a knowledge of what each is doing. A realization of another's problems is often a fertile source of suggestions for subjects of research. The scientific branches, the laboratory men, are often greatly aided by contact with the difficulties of the clinicians, and the latter often point out unsuspected uses of great value for apparently sterile discoveries.

The diseases encountered by the surgical urologist are most often closely intertwined with complicating or secondary lesions in which the internist's help is required—and the more each of these varied interests can know about the other the better it should be for all.

It is therefore evident that some common meeting place is extremely desirable—some medium in which all types of papers upon the field of common interest may appear—archives of Urology—historical, embryological, anatomical, biochemical, pharmacological, pathological, bacteriological, surgical and medical, experimental and clinical.

Such is what we hope to accomplish in THE JOURNAL OF UROLOGY, and we bespeak for it the support and active assistance of all who come within the wide scope of its work.

Realizing that authors may often desire to publish their work also in one of the more special journals, we will be glad to allow this if made simultaneously. Wishing to stimulate investigation, we are fortunate in being able to make use of the generosity of a friend in the shape of a "Research Fund," which will be utilized to assist worthy authors of the most meritorious research papers, to be decided by a special editorial committee.

HUGH HAMPTON YOUNG.

STUDIES ON THE GROWTH OF CELLS

THE CULTIVATION OF BLADDER AND PROSTATIC TUMORS OUTSIDE THE BODY

MONTROSE T. BURROWS, J. EDWARD BURNS AND YOSHIO SUZUKI

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Although numerous workers have attempted to cultivate human tumors from different parts of the body, the cultivation of bladder and prostatic tumors has not been undertaken up to the present time. Cellular activity has been observed in but a limited number of the cultures of human tumors which have been tested and those which have been observed to grow have shown few peculiarities which have aided in a better understanding of the conditions which initiate or regulate the growth of these cells.

During the last few months we have studied the cultures of twelve tumors of the bladder and the prostate. The method used consisted in brief in placing small fragments of the tumor tissue (1 mm. in diameter) in a layer of medium (0.5 mm. in thickness) on the surface of a cover glass, inverting over this a hollow ground slide, and sealing it in place with vaseline and paraffin. The culture thus prepared were incubated at 37°C.

The media used have been plasma prepared from the blood of the patient from which the tumor was removed, plasma from the blood of normal individuals and a medium consisting of agar, 0.25 per cent, dissolved in isotonic sodium chloride, or isotonic sodium chloride and ascitic fluid. No difference was noted in the cellular activity in the cultures whether the plasma used as medium was obtained from the first or the second source and the activity was as great in the agar media as in the plasma.

Of the twelve tumors used for these cultures seven were clinically malignant bladder papillomata; one, a benign bladder tumor; two benign hypertrophy of the prostate and two prostatic tumors, each of which showed one portion typically benign hypertrophy, the other part having undergone a carcinomatous change. Besides these, one series of cultures of normal bladder epithelium was also tested. Of the seven malignant bladder tumors cultivated one only failed to show cellular activity in the first twenty hours. This tumor had been removed after the application of a strong solution of cocaine. The cultures of the benign tumor, on the other hand, have shown no cellular activity either in the first or the second transplants. The general structure of this tumor is illustrated in figure 1. It is a benign polyp.

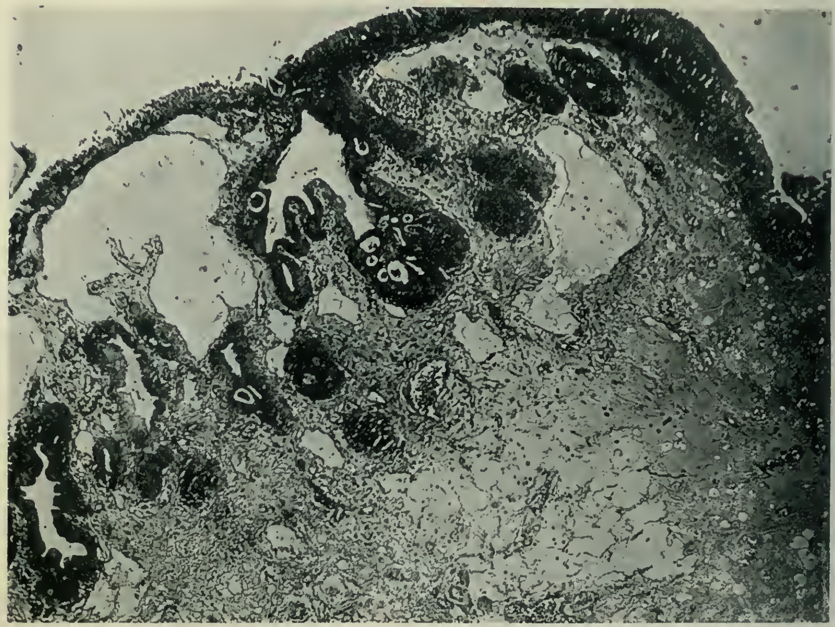

Fig. 1. A Section of the Benign Polyp, Fragments of Which Were Used for Culture

All of the cultures of the bladder tumors were infected with bacteria. However, previous to the time that the bacteria became very numerous the tumor cells showed activity except in the two instances noted above. The type of this activity is shown in the case of Tumor A_{11} (fig. 2) in figures 3 and 4.

A number of the fragments from these cultures were transplanted at the end of twenty hours from the first medium into a fresh drop of the same medium. The plasma clots were liquefied in the original cultures and the transplants very soon after they were incubated. The liquefaction was slightly more rapid in the original cultures than in the transplants. It is impossible to say to what extent the bacteria aided in this liquefaction.

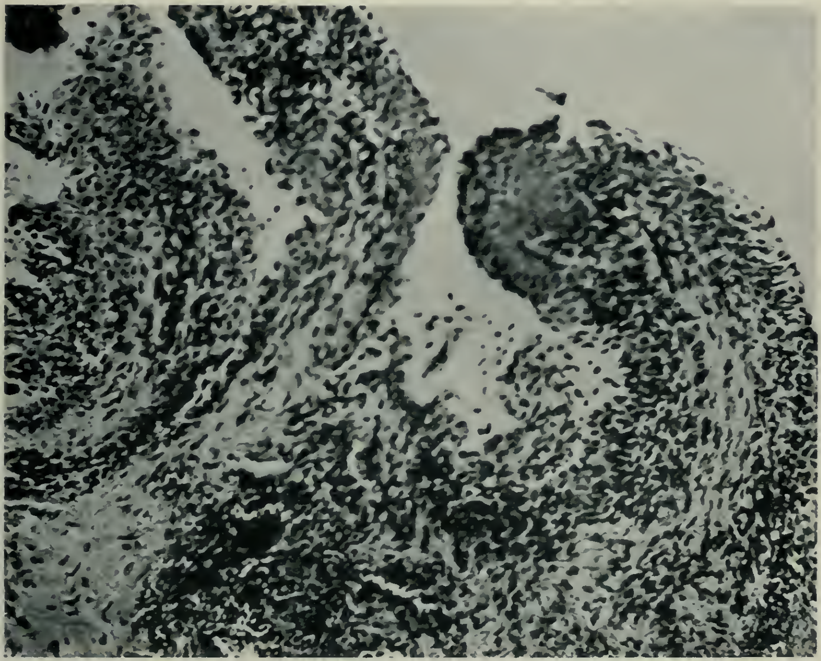

Fig. 2. A Section of the Malignant Bladder Papilloma, Fragments of Which Were Used for Cultures

This liquefaction of the plasmatic medium was noted also by Carrel and Burrows (1) in cultures of human tumors and normal human tissues. The cells failed to show activity in a large number of instances. It was thought that this failure was the result of the liquefaction of the clot or the destruction of the solid medium necessary for the activity of the cells. They noted a moderate cellular activity, however, in a few of the cultures of a giant cell sarcoma of bone. The media had also undergone liquefaction about the fragments of this tumor. This in itself would make it seem that liquefaction of the plasma need not inhibit the activity of the cells.

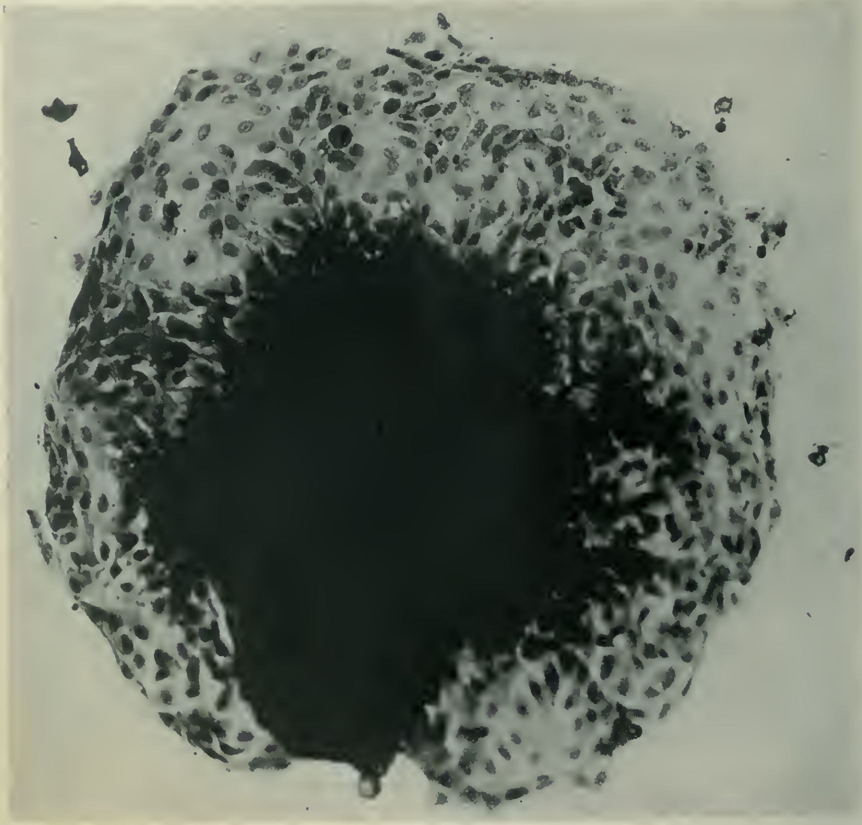

Fig. 3. A Tip of a Papilla of the Malignant Bladder Papilloma (Fig. 2)

After 20 hours' incubation in a culture medium of blood plasma. The pedicle of the papilla is shown at the bottom of the figure. The epithelial membrane surrounds the papilla, except at this point.

One of us, Burrows, during the last few years has again studied a number of human tumors as well as a number of normal human tissues at the General Memorial Hospital, New York City (2).

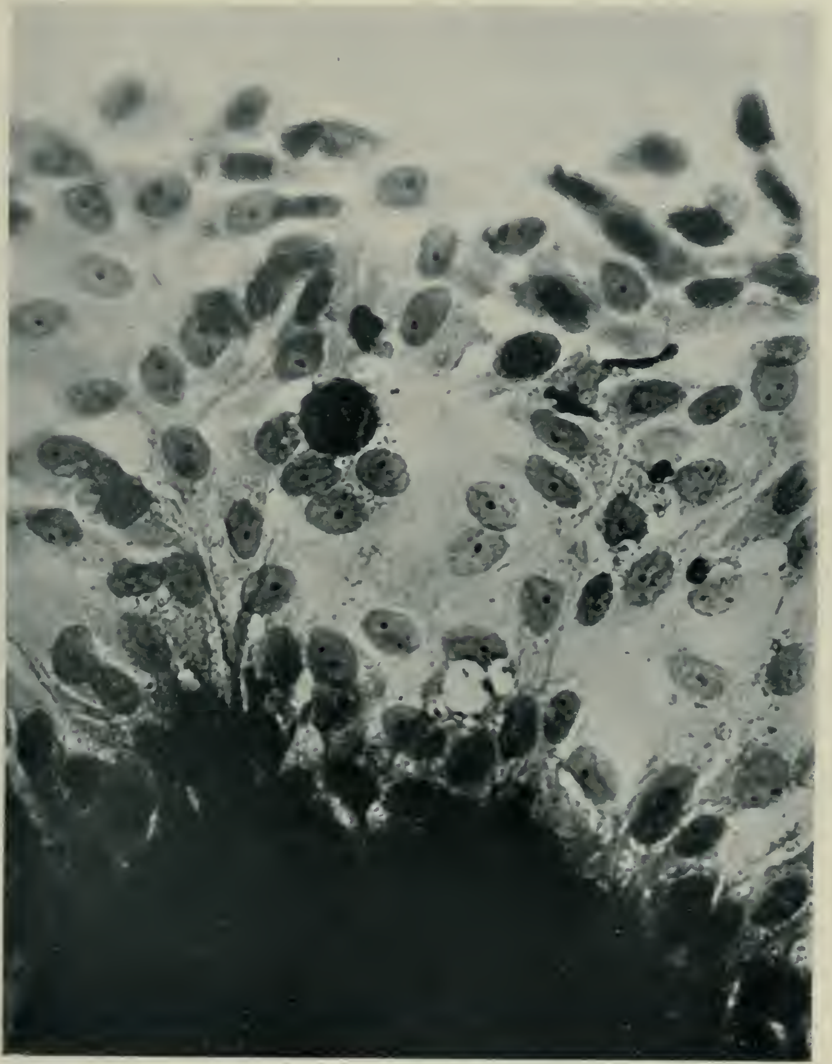

FIG. 4. A HIGH POWER PICTURE OF A SMALL AREA OF THE PERIPHERY OF THE ZONE OF CELLULAR ACTIVITY SHOWN IN FIGURE 3

The tumors studied included a number of lymphomata, breast carcinomata, sarcomata of bone, malignant tumors of the ovary melanomata and a glioma. The normal tissues studied were fragments of connective tissue and arteries removed from normal men at operation for the repair of hernia. The plasma was liquefied about all the fragments of normal tissue which were studied and a number of the fragments of the tumors. There were, however, certain tumor fragments which did not show this change. These were found among the lymphomata and the bone sarcomata. One ovarian carcinoma showed this change to very limited extent. A further study of the normal tissue fragments has shown however, that if the fragments were removed from the first medium at the end of the twenty or twenty-four hours (incubating at 37°C.) to a second drop of plasma that they no longer possessed this property of liquefying it but a characteristic and often an active growth of connective tissue is noted about them. If removed at an earlier time the plasma is again liquefied; when removed at a later date no cellular activity is observed.

The growth of the cells and the changes in the medium was similar to that seen in the cultures of connective tissue of lower animals. The plasma clots undergo contraction with the formation of sheets of fibrin, open fibrin networks or long coarse fibrin fibrillae which radiate out from the fragments into the surrounding medium. The cells migrate out and grow along these fibrin formations. By the use of this method of replantation it was found possible to cultivate the cells of ovarian adenomata, several sarcomata, one glioma and two melanomata. Whether the tumor cells themselves grew from the fragments of the melanomata could not be determined. The cellular activity observed may have been stroma cell activity. Both the stroma cells and the tumor cells grew from the fragments of the other tumors. All the epithelial tumors failed, however, to respond by this method. The plasma was liquefied after each transplant until the cells were exhausted and dead.

This property of liquefying the plasma as shown by the epithelial tumors is not, however, peculiar to them. It is a peculiarity of many epithelial tissues. A piece of frog skin liquefies the plasma for as many as eight transplants or until the cells are dead. A large number of the ectodermal and endodermal tissues of animals have shown similar properties. The liver cells of a few chick embryos have, however, shown an exception to this rule. The plasma was not liquefied in the second transplant and the cells grew actively. Whether certain of the other glandular tissues might not show the same peculiarities has not as yet been determined.

Maccabruni (3) studied fragments of uterine carcinomata and noted the cells to grow in a few of the cultures where plasma prepared from the blood of a pregnant woman had been used as medium. His success he assumed to be due to the particular selection of plasma. Other observers (4) working with Carrel have in later studies noted cellular activity in a number of cultures of human tissues and tumors. In these instances the plasma had not undergone a rapid liquefaction. They note differences in different plasmata and that the addition of Ringer's solution may prevent liquefaction. Burrows planted fragments of each of a number of the tumors which he had studied in as many as seven different plasmata. These included plasmata prepared from the blood of normal men, normal women, women in the early and late months of pregnancy and individuals suffering from chronic syphilis and tuberculosis. There was no definite and sharp relation noted between the growth or liquefaction and the plasmata used. The number of experiments was small—too small to determine this point fully. In a few instances the plasma did apparently kill the cells. These were noted in cultures where the plasma had been prepared from the blood of patients ill with pneumonia. The cells were killed apparently after a few hours in these plasmata; there was, however, no liquefaction. These observations led him to believe that a large number of the variations in the activity of human tumors and normal tissues in the plasma cultures is to be ascribed rather to variations in the tissue fragments than variations in the plasma used.

Other general observations made on the growth of normal tissues would also tend to establish this view (5). The energy-producing substances for the growth of cells in the culture has *not* been shown to come from the medium. The tissue culture in this regard is not comparable to an ordinary culture of bacteria. These substances, on the other hand, are probably derived from the tissue fragment and from the breaking down of cells contained within it. The growth observed may be readily defined, therefore, as a simple transfer of materials from the cells within the fragment or in a less favorable environment to those on the periphery. Proof for this belief has been found in many observations. In plasma culture growth and other forms of activity cease and the cells are exhausted after a few transplants. The sum total of the growth in the various transplants is less than the original mass and it might well be considered as the original mass minus the energy of transfer. Again cells may grow actively from fragment of tissue placed in a medium of simple isotonic sodium chloride or Ringer's solution which contains no energy-producing substances.

In a tissue culture an isolated cell will not grow. Isolated epithelial cells, lymphocytic and leucocytic cells show very little or no activity. Connective tissue cells show movement. When isolated in a drop of liquid plasma they round off. With the clotting of the plasma and after a variable latent period they are seen to send out processes, assume stellate or spindle-shapes. They may migrate two or three cell lengths. At this time they show vacuolation and exhaustion.

The growth of cells is seen only about fragments of tissues. When other conditions are equal this growth is proportional to the size of the fragments. It is seen to take place actively only when the fragments are compact and about 0.3 or 0.4 mm. in diameter. This particular relation holds when the fragments are no greater than 1 mm. in diameter. From fragments of this size the growth is maximum excepting in the case when thin slabs are used.

The growth of connective tissue cells is again influenced in the culture by the presence of muscle or epithelial cells within the fragment. If an active liquefaction of the clot does not proceed and prevent in a great measure the growth of the cells the growth of the connective tissue is most extensive about fragments containing these cells. These more highly differentiated cells break down apparently at the expense of the connective tissue cells.

A careful study of these cultures by serial sections after a growth of cells has taken place has shown the whole mass of cells in the center of the fragment to have deteriorated. In many instances they have become reduced to mere shadows.

Other studies have shown that the actively growing embryonal tissues grow readily in liquid media. This growth takes place, however, only when the fragments are brought into intimate contact with the surface of the medium and only when the culture medium is not agitated. Growth is most active when cellular and fragile fragments are placed in a small drop of medium spread in a very thin layer over the surface of a cover glass. About each fragment, according to its content, is seen either a growth of mesenchyme cells or the formation of membranes or sheets of epithelial cells.

These cells do not move out directly into the medium but along or near the cover glass or lower free surface of the medium. Previous to this growth, however, the lower surface of the medium in many of these cultures is seen to change. The surface becomes fixed and currents cannot be set up easily.

It is interesting that these cells do not grow directly in contact with the cover glass nor directly in contact with the lower surface of the medium, but always in a plane just beneath these surfaces. If the same cells are broken loose from this apparent plane of contact and immersed in the liquid they round off and show no further activity. If pushed back into this plane they again flatten out in a passive fashion and may show active growth.

These observations show that growth takes place only along one plane in the culture. The passive flattening of the cell suggests that a surface exists here and this surface must have formed from the flowing out of substances from the fragment.

Although these facts had clearly shown that a change had taken place at the surface of the medium and they indicated that the food materials probably diffused along this surface, in only a very few cultures studied could one see that a definite layer of substance existed here. The refraction of the substance was quite similar to that of the underlying medium.

In the light of these observations a study of the bladder tumors became of interest. In all the cultures of the bladder tumors, malignant and benign, as well as the cultures of normal bladder epithelium, the plasma clots underwent liquefaction. The failure of the growth of cells from the fragments of the benign polyp and normal bladder epithelium is not necessarily unique. Although actively growing embryonal tissues are seen to grow in liquid media little or no cellular activity has ever been seen about fragments of normal adult tissues of either man or animals in these media. On the other hand, many of these tissues grow readily in plasma clots.

The growth of the malignant bladder tumor cells in these cultures was preceded always by the formation of a definite membrane over the surface of the liquefied medium. In these cultures this membrane was homogeneous but quite easily seen. It contained visible granules; it was very tough. The surface that it covered could not be easily disturbed by shaking. It frequently formed over the lower surface of the medium as well as near the cover glass. In many of these cultures the layer of medium was thick. It was along the surface of this membrane that the cells moved out apparently from the fragment. In these cultures as in the cultures of embryo chick tissue, with a few exceptions, the line of demarcation of this surface zone and the underlying medium was not made out. Small fragments of tumor cells floating in the medium coming in contact with it flatten out.

As to the mechanism of the formation of these membranes no direct observations have been made. They form generally very early in the life of the culture, often apparently during the liquefaction of the medium.

In many of the cultures of bladder tumors the sheets of cells which are seen about the fragments form by a simple migration of cells from the fragment. In other cultures the area covered by cells is very large; too large to be accounted for by migration alone. Growth here must have taken place although mitosis was not observed.

Besides these cultures of fragments of bladder tumors, fragments were also taken from two hypertrophied prostates which contained areas of carcinomatous change. Membranes formed and the cells showed movement (fig. 6) and slight evidences of growth about fragments taken from the carcinomatous portion of one of the prostatic tumors (fig. 5). No change other than liquefaction was noted about the fragments taken from the benign portions. Cultures of fragments of other hypertrophied prostates have given the same negative results.

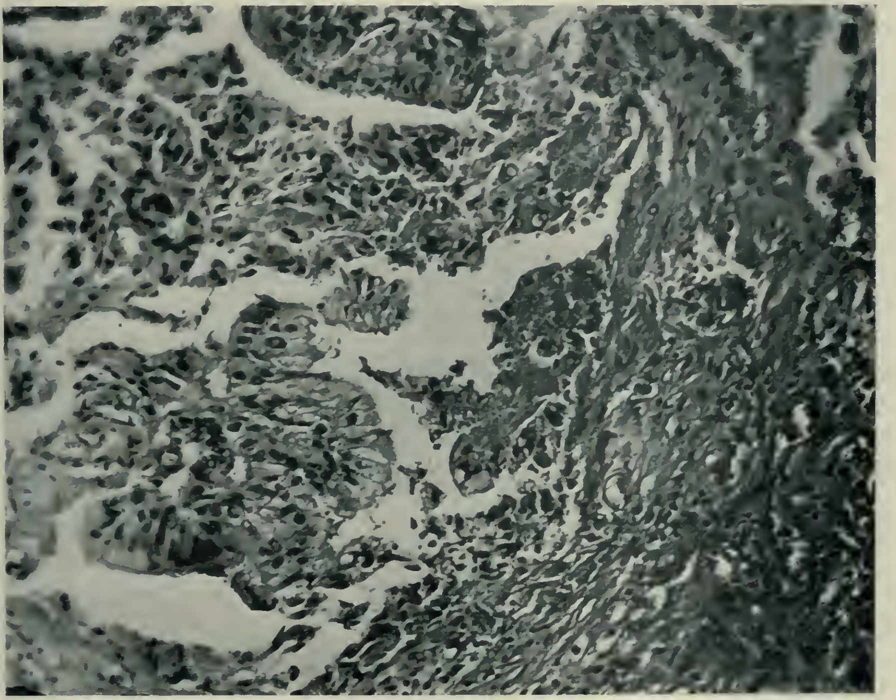

Fig. 5. A Section of the Malignant Portion of the Prostatic Tumor, Fragments of Which Were Used for Cultivation

It was interesting in the case of the other hypertrophied prostate showing carcinomatous change that no activity was observed about either the fragments taken from the carcinomatous or benign portions. This prostate had been treated with radium for four months previous to its removal.

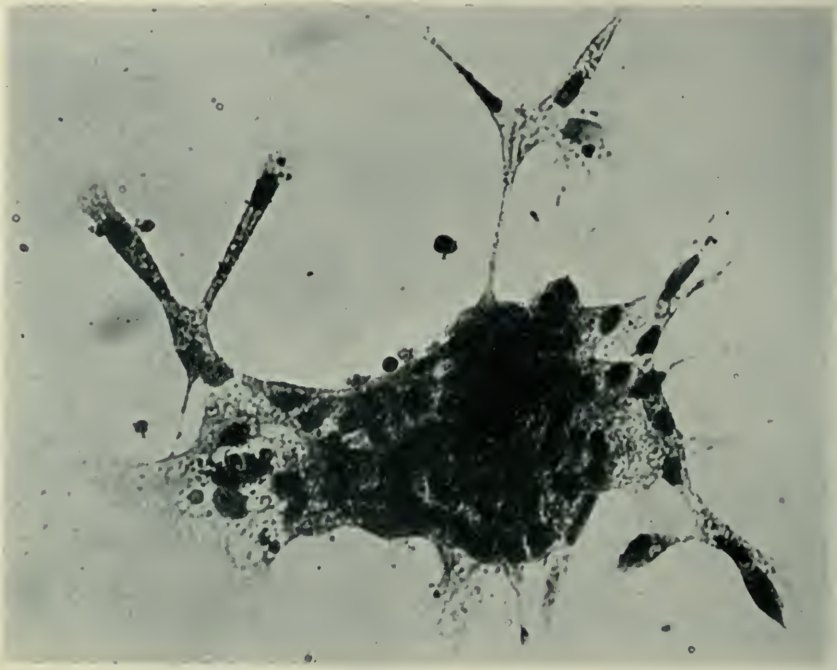

Fig. 6. Migrating Malignant Prostatic Tumor Cells Obtained from Tumor, Figure 5

SUMMARY

These observations have shown facts which may prove important for a better understanding of the conditions essential for the growth of body cells and the general structure of these cells. In none of the cultures of the benign tumors was any cellular activity noted; on the other hand, all of the cultures of the malignant tumors showed marked cellular activity excepting the two instances above mentioned. This activity was observed in a large percentage of a series of cultures from each malignant tumor and occurred in some of them as early as five hours and in all within twenty hours after their preparation. These facts indicate that this method may be important in determining the malignancy, following the course of treatment and studying the biological properties of these tumors.

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DOUBLE URETER AND KIDNEY, WITH CALCULOUS PYONEPHROSIS OF ONE HALF; CURE BY RESECTION. THE EMBRYOLOGY AND SURGERY OF DOUBLE URETER AND KIDNEY

HUGH H. YOUNG and EDWIN G. DAVIS

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

During recent years we have had in our clinic several cases of double kidney and ureter in which one portion of the double kidney was diseased. Only one of these cases has come to operation, and a careful study of the literature shows that although the condition is not very rare, its recognition and cure by operation is extremely rare. In fact, we can find no satisfactory report of any such case, and on this account it seems quite timely to report in full the following case in which a large branched calculus, occupying the upper half of a double kidney, was recognized and the condition cured by resection of the upper diseased half of the kidney with its special pelvis and ureter. Through the kindness of Dr. Franklin P. Mall, who placed at our disposal the complete series of embryos of the Carnegie Embryological Institute, and the assistance of Dr. George L. Streeter, we have been able to study the early embryology of the ureter and to make drawings and microphotographs which illustrate the development of this frequent and interesting anomaly.

Case report

History. The patient, a man of 57, was admitted on April, 7, 1916, to the James Buchanan Brady Urological Institute, complaining of a pain in the left flank. The pain was dull and aching in character, was increased by exertion, and had been present, with exacerbations and remissions, for ten years. There was no history of any attack resembling renal colic. He complained also of frequency of urination, voiding about every two hours by day and night. Pain in the back together with frequency and some burning on urination were his only symptoms. The patient could not name the exact date of onset but stated that symptoms had been present for at least ten years, during a great part of which time he had been unable to work. His family history and past history were unimportant.

Examination. The general physical examination was practically negative. The patient was a well-nourished, middle-aged man. With the exception of a few fine crackling râles audible on deep inspiration over the posterior base of each lung, no abnormality of the chest or abdomen was made out. Neither kidney could be felt, nor was there any tenderness in either kidney region. The urine showed a trace of albumin and a heavy sediment which in the stained specimen was seen to be made up of pus with numerous bacilli.

X-ray. Neither renal shadow was to be made out but in the region of the upper pole of the left kidney was seen a large irregularly branching calculus, as shown in figure 1. No shadow was seen in the region of the right kidney or of either ureter.

Cystoscopy and ureteral catheterization. There was no residual urine and the bladder capacity was normal. The cystoscope, which was easily inserted, showed a bladder mucosa everywhere somewhat reddened and inflamed, and an elevated and thickened trigone. There was no stone or diverticulum. The ureteral catheters, which met with no obstruction, were passed up each ureter a distance of 15 cm. The urine obtained from the right catheter was macroscopically clear and the centrifuged specimen showed only a few red blood cells, while that from the right was purulent. Phenolsulphonephthalein (6 mgm., injected intravenously) appeared on either side in four minutes, the output after thirty minutes being 20 per cent from the right side and 10 per cent from the left. The urea concentration in the urine excreted by the right kidney was twice that from the left.

Pyelogram. Thorium solution (15 per cent), prepared according to the method described by Burns (1), was injected by the gravity method through each ureteral catheter. The pyelogram showed, on the left side, a double renal pelvis with a bifurcation of the ureter at the level of the third lumbar vertebra, and about 9 cm. below the lower pelvis (fig. 2). The upper larger pelvis was completely filled by the calculus mentioned above. The lower pelvis was slightly smaller than normal and the calices were not dilated. The pyelogram on the right side showed a normal pelvis with the exception of an apparent kink at the uretero-pelvic junction, artificially produced by the ureteral catheter.

Diagnosis. Left bifid ureter with double pelvis and kidney; calculus in upper portion; lower portion probably normal. Right kidney normal.

Operation. Young. April 14, 1916. Under nitrous-oxide, oxygen and ether anesthesia, the left kidney was exposed through an oblique lumbar incision. The lower portion of the kidney was found to be normal in appearance, a little larger than a half of a normal kidney, and only moderately adherent to the fatty capsule. The ureter coming from the lower portion or segment was easily exposed and was found to be slightly dilated and thickened. The upper segment of the kidney, which was exposed with some difficulty on account of dense adhesions to the fatty capsule, was much larger than the lower, was nodular and inflammatory, and through the thin shell of renal tissue could be felt a large, irregularly shaped calculus, almost entirely filling the interior. Demarcating the two portions of the kidney was a slight but distinct furrow, the upper and lower portions of the kidney being quite different in appearance. Figure 3 shows the kidney exposed. In order to avoid the danger of injury to the vessels of the lower normal portion, by attempting to dissect the dense fibrous mass which constituted the pedicle and which surrounded the blood supply of both portions, the operator divided and ligated only a small portion of the upper part of the pedicle, and then made a transverse incision through the kidney just above the junction of the two segments, not cutting into the normal kidney tissue (fig. 4). After this it was a comparatively simple matter to isolate and ligate the entire blood supply to the upper segment. A moderate amount of bleeding from the cut surface of the remaining kidney tissue was effectually controlled by placing four mattress sutures of catgut, and tying while the edges were approximated between the thumb and forefinger, as shown in figure 5. After division and ligation of its ureter about 0.5 cm. above the point of bifurcation, the upper diseased segment was removed, leaving in situ a normal half kidney with undisturbed blood supply, pelvis and ureter. The incision was closed with catgut and drained. The patient stood the operation well.

Pathology. Examination of the specimen removed showed that it consisted of a mere thin-walled sac of fibrous tissue, microscopical sections from which showed a complete absence of kidney tubules. Almost entirely filling the sac was a large branching calculus shown in figure 6.

Post-operative history. The immediate convalescence was uneventful. On the twelfth day the last drain was removed, leaving a small narrow sinus which persisted, with a scant mucoid discharge, until the thirty-fourth day, when a urinary fistula developed. On the following day the patient's temperature rose to 103° and remained irregularly elevated for three days, then returning to normal and remaining so, the urinary drainage ceasing on the day after the temperature dropped. Two weeks later, the patient was discharged from the hospital with the incision entirely healed and the temperature normal. Urine examination at this time showed still a trace of albumin and only a very few pus cells. A thorium pyelogram made on the day of discharge showed, on the left side, a pelvis slightly smaller than normal and with normal calices; just as before operation (fig. 7). The stump of the excised ureter was not visible. The phenolsulphonephthalein test showed a secretion of 3 per cent from the left side in half an hour, and 15 per cent from the right. The urine from the right side was clear, while that from the left still showed a few pus cells and bacilli.

On August 10, four months after operation, the patient returned for examination. His general condition was excellent, he was entirely relieved from symptoms, and able to resume his work. Ureteral catheterization done at this time showed a clear, uninfected urine from each kidney. The phenolsulphonephthalein output after thirty minutes was 20 per cent from the right side and 5 per cent from the left.

FREQUENCY AND SURGICAL IMPORTANCE OF RENAL ANOMALY

Anomalies of the kidney and ureter occur more frequently than is generally appreciated, and among such kidneys a relatively large number show pathological changes. In other words, malformation predisposes to disease. Botez (2) demonstrated this by statistical study. Basing his calculations upon 51,504 autopsy records, he found the frequency of horseshoe kidney to be 1 in 715, while in a series of 1000 kidney operations the proportion was 1 in 143, a percentage five times as great. From this he concluded that a horseshoe kindey is more apt to become diseased than a normal kidney. Robinson (3), among fifty collected specimens of duplicate ureter, found that hydroureter (of one ureter) occurred in 24 per cent. In a series of 24 cases of explored double kidney and ureter, to be cited below, the pathological process was located in the upper kidney segment in 19 instances. Judging from this uneven percentage it is fair to assume that partial obstruction of the superior ureter, due to its position with respect to the lower kidney segment and to the kidney pedicle, had been an important factor in producing disease. Girard (4), among 44 cases of ectopic kidney, found 21 hydronephroses. An idea as to the frequency of renal anomaly may be obtained from the studies of Naumann (5), who found 100 anomalous kidneys in a series of 10,177 autopsies; about 1 per cent. This series included only gross renal anomaly, such as fused, ectopic, cystic, atrophic and lobulated kidney. Anomalies of the renal vessels are very much more frequent. Papin (6), in examining a series of 324 kidneys, found 64 (exactly 20 per cent) in which there were at least two renal arteries. If 20 per cent of all kidneys possess anomalous arteries, the percentage of individuals with anomalous renal arteries must necessarily be still higher. For a splendid review of the entire subject, dealing with the importance and the frequency of the various forms of renal and ureteral malformation, and including an extensive bibliography, the reader is referred to the complete work and Adrain and Lichtenberg (7).

Ureteral duplication, with double pelvis and kidney, is surprisingly common. It occurs more frequently than all the other forms of gross renal anomaly taken together. Poirer (8), Wagner (9) and Bostroem (10) independently concluded that 3 per cent of all individuals have double or bifid ureter, while Robinson found six instances in one hundred consecutive autopsies. As early as 1878 Weigert (11) had noted the frequency of this anomaly and stated that "more than one case" occurred in every hundred. Four cases of double ureter, out of 165 dissections, were reported by Kerr (12). In examining 60 human embryos, Pohlman (13) found two instances of double ureter, the embryos being 13 and 24 mm. in length respectively. The condition therefore is one which every urologist is certain to encounter, and which should be diagnosed before operation either by cystoscopy or pyelography, in many of the cases.

EMBRYOLOGICAL DEVELOPMENT

In considering the formation of double ureter it is of interest to review briefly the facts known about the early development of the ureter and kidney from the Wolffian duct. It will be remembered that during the embryological development of the higher vertebrates, three successive types of excretory organ (pronephros, mesonephros and metanephros) are formed in the order named, the first two being provisional or temporary, and the third becoming the permanent kidney. All three are of mesodermal origin, being derived from the nephrotomes or primitive segment stalks, a series of mesodermal cell masses extending longitudinally on either side of the neural canal, and lying between the primitive segments and the lateral mesodermal plates. Considered as a whole, these primitive segment stalks make up the nephrogenic cord, the parent structure of all three excretory organs. After the formation of the pronephros, which early takes place from its cranial portion, the nephrogenic cord becomes divided into mesonephrogenic and metanephrogenic portions, the former giving rise to the Wolffian body and the latter, the caudal portion, being destined to form the secreting portion of the permanent kidney.

The pronephros in some of the lower vertebrates is well developed and is the permanent and only excretory organ, while in mammals it is quite rudimentary and may be demonstrated for only a very short period during the life of the embryo. Although its presence in the human embryo is very transient, it has been definitely shown that it exists (Felix (14)), that it occurs only in the region of the first twelve primitive segments, that its development begins before the embryo has reached the 2 mm. stage, and that it has undergone complete atrophy (excepting for its duct, the primary excretory duct) by the time the embryo has reached a length of 5 mm. It has no function and is of importance only in that its duct persists to form the Wolffian duct, the excretory duct of the mesonephros.

The mesonephros or Wolffian body, arising from the primitive segment stalks from the fifth cervical to the third lumbar segments (the mid-portion of the nephrogenic cord), and consisting of a series of glomeruli and tubules opening into a common efferent duct, is the permanent excretory organ in certain fishes and amphibians but undergoes atrophy in man. Its duct, the mesonephric or Wolffian duct, opens into the cloaca (the blind caudal extremity of the intestinal tract) which it reaches at about the 4 or 4.5 mm. stage of embryonic life, as shown in figures 8 and 9. Felix considers that in man the mesonephros does not function as an excretory organ because it is well on its way toward degeneration before the metanephros, or permanent kidney, has sufficiently developed to assume any excretory function that the former might have had. The mesonephros is at the height of its development during the fourth and fifth weeks of embryonic life (Kelly and Burnam (15)) and undergoes atrophy from the eighth to the sixteenth weeks, the duct persisting as the vas deferens in the male and being rudimentary in the form of Gärtner's duct in the female.

The anlage of the metanephros or permanent kidney appears (in an embryo of about 5 mm.) as a budding or evagination from the lower end of the Wolffian duct close to its opening into the cloaca, as shown in figures 10, 15, 16 and 17. The stage of renal development, however, corresponds only approximately to the external measurements of the embryo, and therefore embryos larger than 5 mm. may show no evidence of ureteral buds. Such was the case in embryos 1075 and 873 of the Mall collection, each of which measured 6 mm. This bud is destined to form the ureter, pelvis, calices, and collecting tubules, that is, the entire efferent apparatus, while the secreting portion of the kidney, including Bowman's capsules, convoluted tubules, and ascending and descending loops of Henle, is derived from a mass of mesodermal cells forming the so-called metanephrogenic tissue which, as stated above, has its origin from the caudal portion of the nephrogenic cord. This mass of cells surrounds the tip of the ureter very soon after its evagination, even before the bud has grown a distance equivalent to the diameter of the Wolffian duct, and is shown in figures 18 and 19, the nuclei staining very deeply in sharp contrast with the surrounding mesoderm. These specialized mesodermal cells are also shown in figures 16 and 17 and are seen to form a distinct, almost diagrammatic, mesodermal "cap" covering the bulbous tip of the ureteral bud. The ureteral bud grows at first dorsally toward the vertebral column and then turns and grows cranially, the tip being surmounted or capped by the mass of metanephrogenic cells which accompanies it in its ascent. As early as the 6.6 mm. stage the ureteral tip has become bulbous, the primitive pelvis thus being differentiated from the more slender stalk, the future ureter (figs. 11, 16 and 17) and as early as the 8 mm. stage a bifurcation of the primitive pelvis has taken place, separating it into upper and lower divisions, the first evidence of the calices (figs. 12 and 20). A continued process of outgrowth and branching produces the complete system of calices and collecting tubules. During the ascent of the kidney, changes are taking place in the region of the lower end of the ureter. By a gradual downgrowth of the urorectal septum, which first appears as a saddle-like depression between the allantois and intestine, the cloaca becomes divided into urogenital and intestinal portions, the future bladder and rectum. The series of cloacal models shown in figures 8, 9, 10, 11, 12 and 13, indicates the various stages by which the cloaca becomes divided into separate portions by this coronal septum, which finally reaches the cloacal membrane, dividing the latter into urogenital and anal membranes. The septum passes posterior to the orifices of the Wolffian ducts so that the latter come to open into the urogenital portion. Figure 21, which is a sagittal section passing through the bladder and rectum of a 23 mm. embryo, shows that a pouch of peritoneum (*C*) extends down into the urorectal septum to a point well beyond the entrance of the Wolffian ducts (ejaculatory ducts) into the urethra. This peritoneal pouch subsequently becomes obliterated, and its identical position comes to be occupied by Denonvilliers' two-layered fascia, which in adult life intervenes between prostate and rectum and is of such great surgical importance, both as a cleavage plane in perineal prostatic and seminal vesicle operations, and as a barrier in limiting the extent of malignant disease of the prostate. As early as 1837 Denonvilliers (44) wrote an excellent anatomical description of this fascia, although he did not understand its embryological significance and evidently did not recognize the existence of more than one layer. By a process of dilatation, as shown in figures 11 and 12, the lower end of the Wolffian duct comes to form a portion of the wall of the future bladder, the ureter thus acquiring an orifice separate and distinct from that of the Wolffian duct, which shifts downward and later becomes the ejaculatory duct (fig. 13).

We have stated above that, at about the 8 mm. stage, the blind bulbous tip of the ureter (the primitive pelvis) normally splits into upper and lower divisions, the first evidence of the calices (figs. 12 and 20). There is a general agreement among authors that the formation of incomplete double ureter may be accounted for by a premature or exaggerated bifurcation of the tip of the ureteral bud, the split extending varying distances down the ureteral stalk instead of being confined to the bulbous tip or primitive pelvis (fig. 14). Felix describes this as a "precocious splitting of the ureter," the bifurcation taking place before the formation of the primitive renal pelvis, and the two ureters thus formed ascending parallel to one another. He designates such forms of ureter as "cleft ureter," reserving the term "double ureter" only for those that have separate openings in the bladder. We have seen no case of partial ureteral duplication in which the portion of the ureter nearest the kidney was single and that nearest the bladder double, nor have we found records of any such case either in the pathological or the surgical literature. It would be difficult to explain such a condition embryologically.

Concerning the origin of complete double ureter there is some difference of opinion. Felix considers that such ureters must necessarily arise as separate outbuildings from the Wolffian duct. According to Pohlman, the bifurcation may take place so close to the Wolffian duct that the two ureters acquire separate orifices through the process of dilatation of the caudal end of the Wolffian duct, by which process the latter becomes a part of the bladder wall. Huntington (16) cites a case of bifid ureter with one "perfectly formed pelvis and primary and secondary calices," and the other pelvis incomplete. He considers that since this normal pelvis could have arisen only as the result of a normal development of a normal ureteral bud, the second ureter and pelvis must therefore have arisen as a lateral sprout from the main ureteral stem. It may be stated as a general rule that, in case of complete double ureter, the ureter which has its orifice lowest in the bladder drains the higher renal pelvis, as was pointed out by Weigert as early as 1877. In cases of resection of a portion of the double kidney this crossing of the ureter would be of surgical importance.

ANALYSIS OF CASES IN LITERATURE

Excluding the numerous reported cases of bifid or double ureter demonstrated by autopsy or dissection, and those demonstrated by cystoscopy and by examination of the external genitalia, we have been able to find in the literature, in addition to the case we are reporting at present, twenty-six instances in which this form of anomalous kidney was operated upon. All of these showed complete duplication of the renal pelvis, and grades of ureteral duplication varying from a bifurcation close to the kidney to a complete supernumerary ureter with a separate orifice; and all but two were operated upon because of a pathological process located in the anomalous kidney. In the two exceptions, cases of Stammler and Josephson, the operation was undertaken merely on account of the incontinence produced by the supernumerary ureter opening externally, there being no lesion in the kidney itself.

Josephson's (17) patient was a girl of eighteen who had had incontinence since birth due to a supernumerary ureter opening near the external urethral orifice. After a correct diagnosis he was able to cure the incontinence by exploring a left double kidney and resecting the upper portion which was about "the size of a hen's egg," leaving in situ a lower normal portion the size of a normal kidney. In Stammler's (18) case there was bilateral double ureter, each anomalous ureter opening into the vagina, and, in accordance with Weigert's rule, draining the upper pelvis of a double kidney on either side. Both kidneys were explored. On the right side the anomalous ureter was sectioned and the two renal pelves anastomosed. On the left side an anastomosis was considered inadvisable on account of the small size of the upper pelvis, and therefore a part of the upper half of the kidney was resected. The incontinence was cured.

In all of the remaining twenty-four cases the operation was undertaken on account of a pathological condition which was primarily confined to one segment of a double kidney, and in all but three (Lange (19), Chute (20), Linck (21)), the remaining segment was normal at the time of operation. There were sixteen cases of pyonephrosis (four complicated by stone), four of tuberculosis, three of hydronephrosis and one of "acute surgical kidney" (Lange). It is of interest to note that in nineteen instances (practically 80 per cent) the pathological condition was located in the upper segment. In four the lower segment was involved, while in the remaining one the seat of the disease was not mentioned. In two instances (Steiner and Franke) the operation was pyelotomy. Steiner (22) drained a pyonephrotic sac involving the lower portion of a double kidney. Franke (23) drained a hydronephrosis of one pelvis of a double kidney and divided an anomalous artery which was the cause of the obstruction. In Scudder's (24) case, that of a child twenty months old, there were acute symptoms produced by a huge, dilated, supernumerary ureter which ended blindly. Merely an exploratory operation was done, the child dying soon afterward.

The possibility of an erroneous diagnosis due to an anomalous ureter is nicely shown by the case reported by one of us (Young (25)) in 1903. The patient, a man of 54, with a history of pyuria of several years' duration, and who had had one attack of left-sided renal colic with passage of calculus two years before admission, showed, as a result of ureteral catheterization, clear normal urine from the left kidney and purulent urine from the right. The X-ray plate showed a large calculus in the region of the right kidney with no shadow on the left. With a negative X-ray examination and normal urine from the left side, the conclusion was that the left kidney was normal, and therefore a right nephrotomy with removal of calculus was done by Dr. Finney, the patient dying two days afterwards from anuria. As revealed by autopsy, the left ureteral catheter had happened to enter the normal branch of a bifid ureter which led to a lower normal kidney segment. The upper half of the left kidney was pyonephrotic and contained a large calculus which was not revealed by the X-ray examination because the plate had happened to be placed too low. In figure 22, a drawing by Mr. Broedel of the autopsy finding, the limits of the area covered by the X-ray plate are indicated by a slightly darker tone. The mistaken diagnosis was therefore dependent upon curious coexistent pathological and anomalous conditions, taken together with two unfortunate incidents. If the catheter had entered the other branch of the bifid ureter, purulent urine would have been obtained instead of normal urine and if the X-ray plate had been placed higher the large calculus would have been discovered. At that time pyelography had not been introduced.

The remaining twenty cases of double kidney were all nephrectomies, and in all but one (Albarran (26)) the operation was complete nephrectomy. In three of them (Lange, Chute, Linck) the second portion of the kidney was said to be "obliterated," "functionless" and hydronephrotic respectively. Nephrectomy was therefore the correct procedure. Sixteen of the double kidneys, however, were half normal, and would have afforded an opportunity for partial nephrectomy with preservation of a normal portion. The cases were those of Brewer (27), Bruci (28), Dumitreanu (29), Dobrotworsky (30), Floderus (31), Heymann (32), Key (33), Kusnetzky (34), Marion (35), Martin (36), Rafin (37), Summers (38), Stolz (39), Tschudy (40), Wille (41) and Wulff (42). In this series of twenty nephrectomies the diagnosis of ureteral duplicity was made before operation in two instances only, while in eighteen the condition was accidentally discovered during the course of the operation, or later by an examination of the pathological specimen.

There remains the case of Albarran, the only one in the series in which the normal portion of the kidney was preserved. We find Albarran's brief mention of this case in the transactions of the ninth session of the Association Française d'Urologie (1905), in a discussion following a demonstration by Nicolich of a pathological specimen showing a supposed persistent Müllerian duct in the male. In this discussion Albarran considered the specimen of Nicolich to be in reality one of supernumerary ureter opening into the prostatic urethra, and he then briefly described a similar case of his own in which he had removed the upper half of a double kidney for pyonephrosis. Apparently there was no stone. The operation was undertaken to cure a renal fistula resulting from a previous operation, and the abnormality was discovered accidentally and not by previous diagnostic methods. Albarran has made no official report of this case but we quote his brief remarks in their entirety in the following literal translation.

> "The patient was a young man of 26 years, who in Italy had had a nephrotomy for pyonephrosis, resulting in a fistula which discharged a small amount of urine and much pus. During the operation which I undertook to cure the fistula I found two kidneys, the one above the other, both firmly adherent, and demarcated, the one from the other, by a furrow. The upper kidney, the smaller, was almost destroyed by the pyonephrosis. After having cut the renal tissue at the level of the furrow which separated the two kidneys, I extirpated the superior kidney, which had an independent pedicle, together with its pelvis and a portion of the ureter, very dilated and thin. I do not know where the ureter ended below but it certainly did not go into the bladder which I have carefully examined with the cystoscope."

It is unfortunate that we have no illustrations and no adequate record of this case. As to the exact condition found at operation, the presence or absence of stone, the cause of the pyonephrosis, the point of junction of the two ureters and as to the convalescence and the ultimate result, we are not informed.

We find a brief mention of three operations upon presumably similar cases by Braasch (43) as follows: "Bisection of such a kidney was performed successfully in three instances by W. J. Mayo after the clinical diagnosis had been made." Other than this one sentence, no further report in this country has been found.

CONCLUSIONS

The case reported above is apparently unique in that it is the only such case to be found fully reported in the literature.

The condition of double kidney and ureter is not rare, and the upper half is most often the seat of disease; its surgical importance is therefore great.

The advent of ureteral catheterization, radiography and pyelography has made the diagnosis easy and we should expect the discovery of more cases in the future.

The radical cure by excision of the diseased half of the kidney with its pelvis and ureter is undoubtedly the method of choice.

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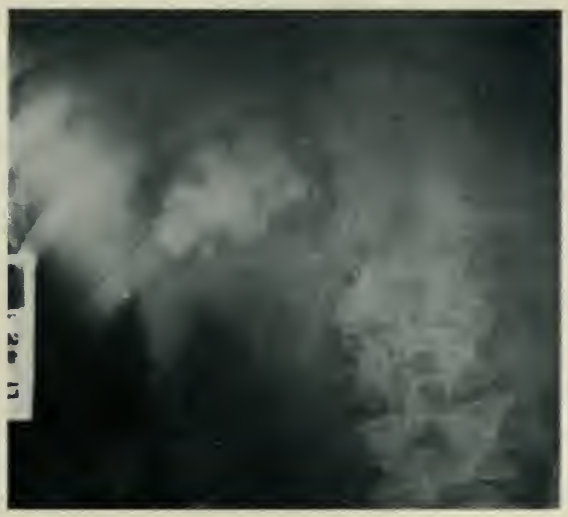
PLATE 1

Fig. 1. Radiogram showing large, branching renal calculus, afterwards found to be located in upper half of double kidney.

Fig. 2. Thorium pyelogram showing right bifid ureter and double kidney. Calculus in upper pelvis.



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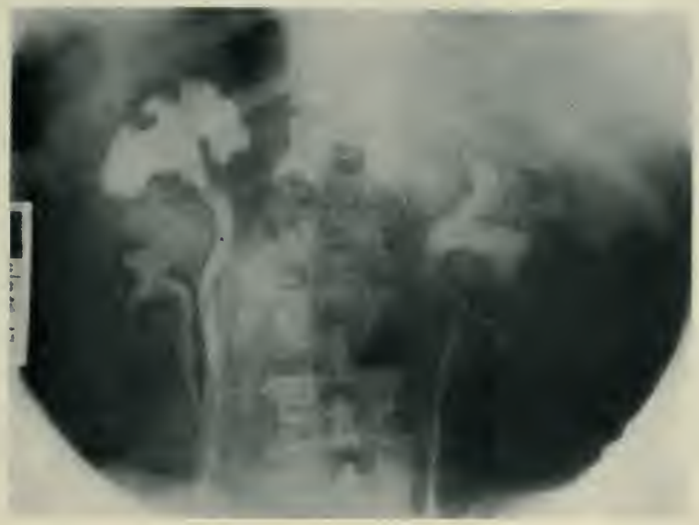


2

PLATE 2

Fig. 3. First stage of operation, showing the double kidney exposed. The upper large pyonephrotic portion is demarcated from the lower normal portion by a furrow. The point of bifurcation of the ureter is diagrammatically indicated in dotted lines.

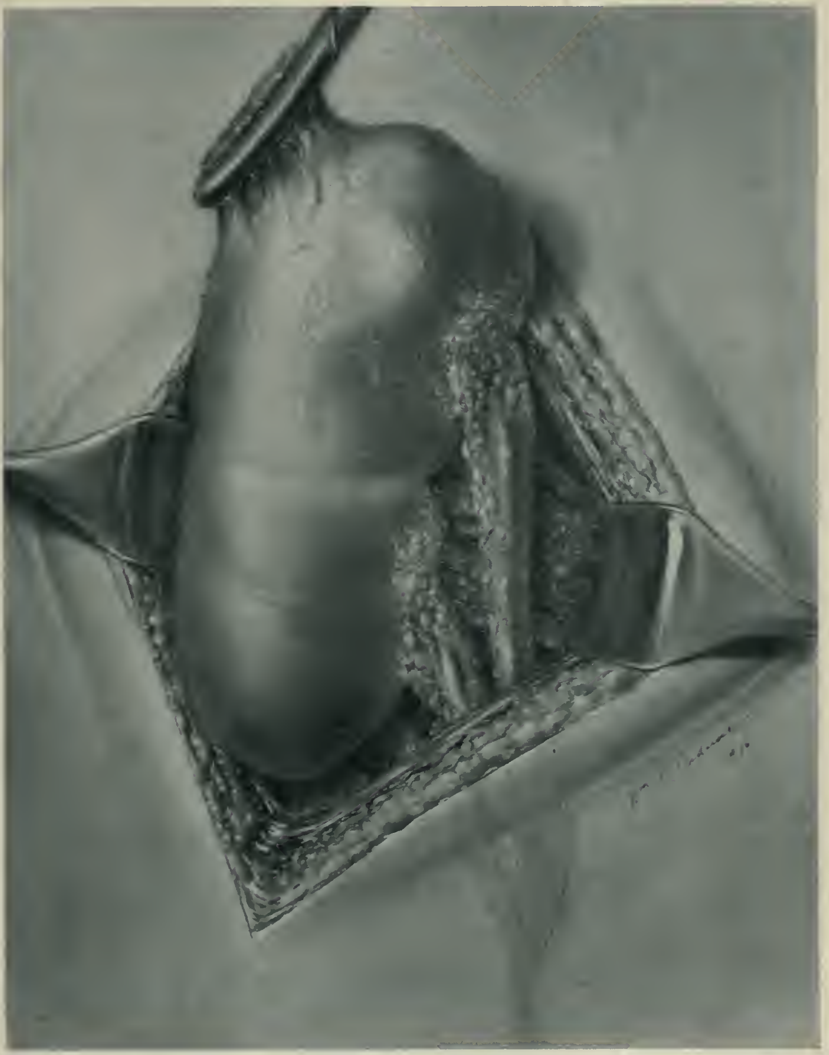


PLATE 3

FIG. 4. Second stage of operation. The two segments of kidney tissue have been separated by a transverse incision just above the level of the furrow.

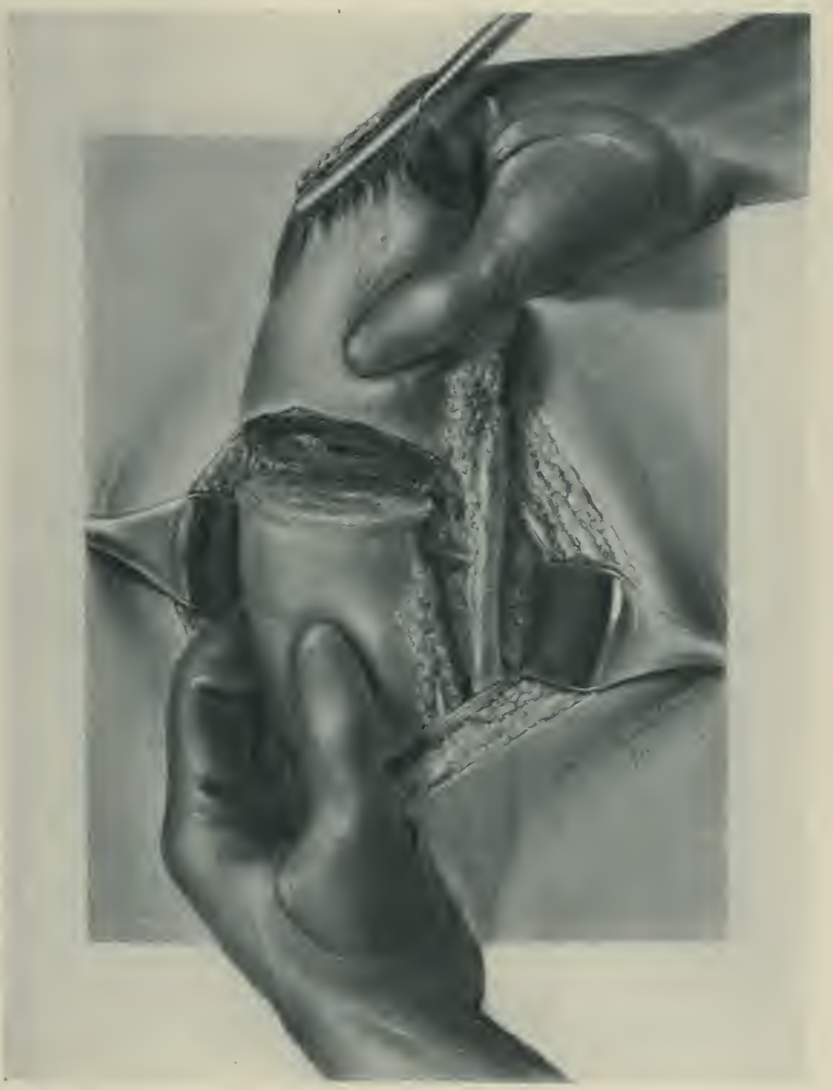


PLATE 4

Fig. 5. Third stage of operation. The diseased segment has been removed, its ureter ligated and the hemorrhage from the normal portion controlled by mattress sutures.

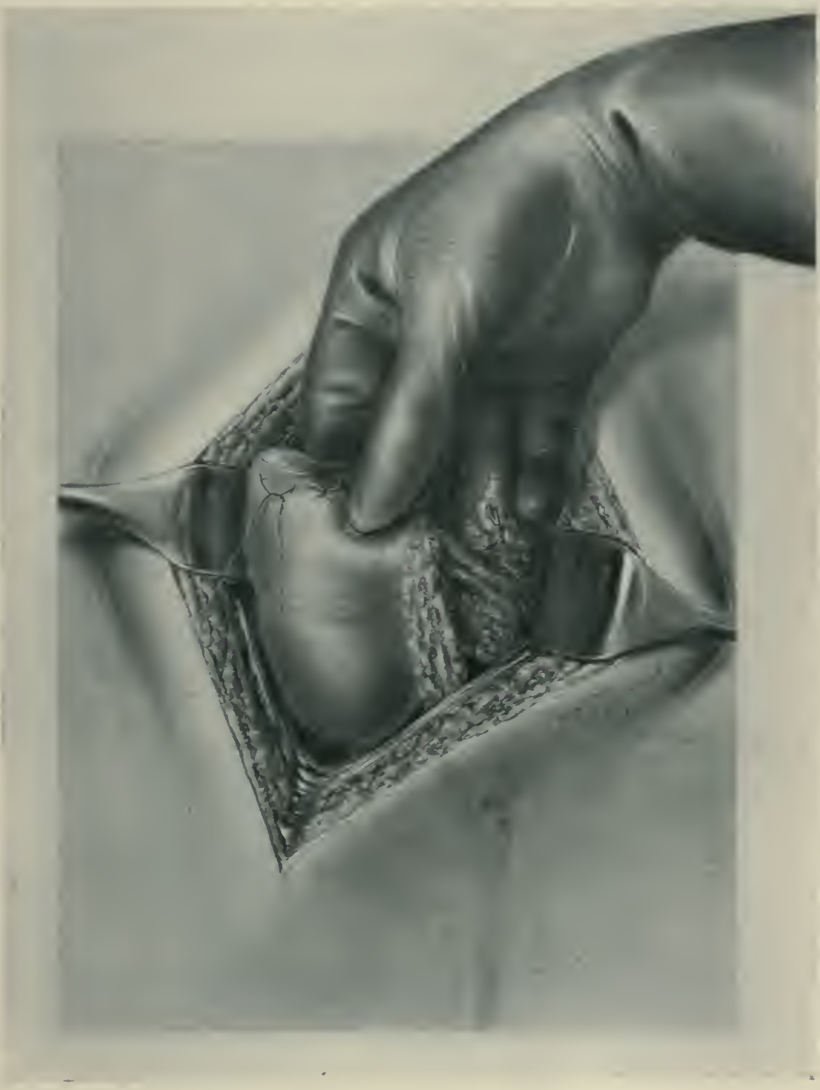


PLATE 5

Fig. 6. Calculus after removal from upper half of double kidney.

Fig. 7. Thorium pyelogram made after removal of upper calculous pyonephrotic portion of double kidney. Contrast with figure 2.

6

7

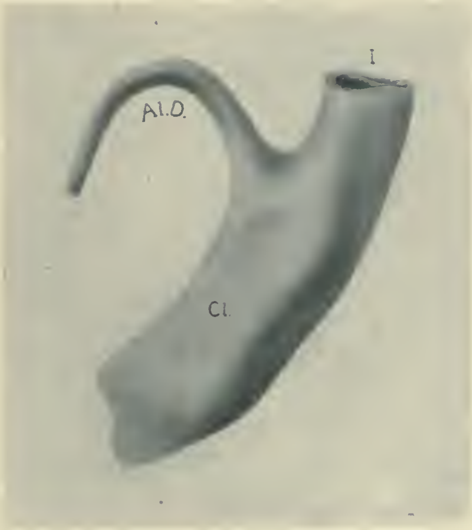
EXPLANATION OF FIGURES 8 TO 21, INCLUSIVE

An., Anus
Ao., Aorta
Al.D., Allantoic duct
A.M., Anal membrane
B., Bladder
C., Coelom
Cl., Cloaca
Cl.M., Cloacal membrane
E.D., Ejaculatory duct
I., Intestine
M., Mesonephrogenic cells
N.C., Neural canal
O.M.P., Omphalo-mesenteric plexus
P.C.V., Posterior cardinal vein
P.P., Primitive pelvis
R., Rectum
U., Ureter
U.B., Ureteral bud
U.M., Urogenital membrane
U.R.S., Urorectal septum
W.D., Wolffian duct

PLATE 6

FIG. 8. Cloaca of a 3 mm. human embryo (× 66). The Wolffian ducts have not yet developed in this region. (After model by Keibel.)

FIG. 9. Cloaca of a 4.2 human embryo (× 50). The Wolffian ducts have appeared, and enter the cloaca on either side. (After model by Keibel.)



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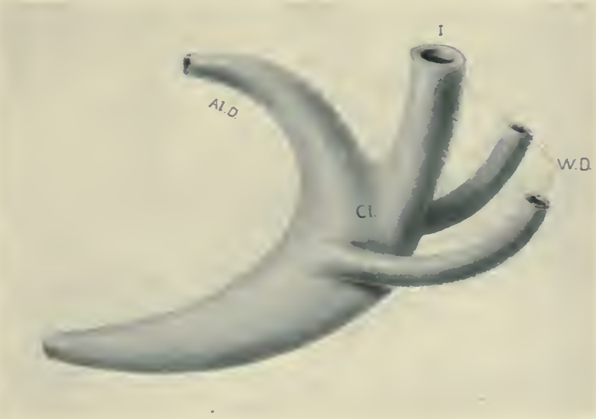

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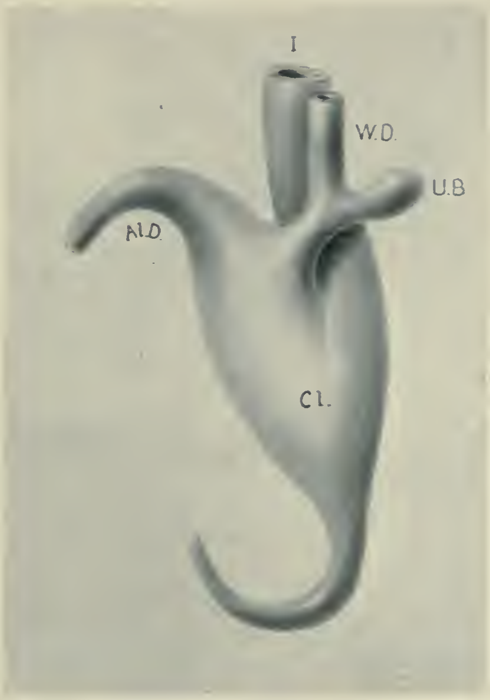
PLATE 7

FIG. 10. From a 6.5 mm. human embryo (× 66). The ureteral bud is seen springing from the Wolffian duct close to its opening into the cloaca. The beginning separation of the cloaca into intestinal and urogenital portions by the urorectal septum has begun. For the sake of clearness, the right Wolffian duct has been omitted in this drawing and in those following. (After model by Keibel.)

FIG. 11. From a 7 mm. human embryo (× 66). The urorectal septum has separated the cloaca into two distinct portions, the Wolffian duct opening into the anterior portion. The lower end of the Wolffian duct has become dilated. (After model by Felix.)



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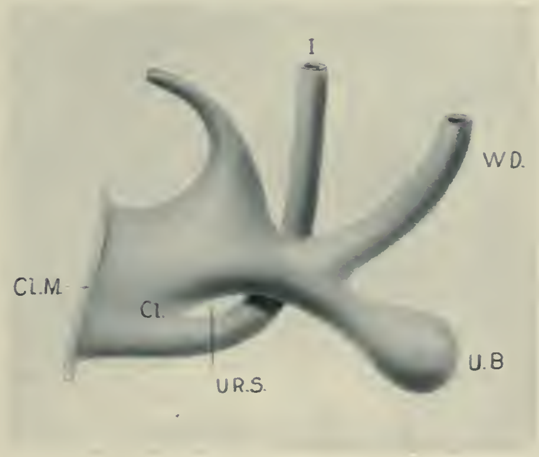

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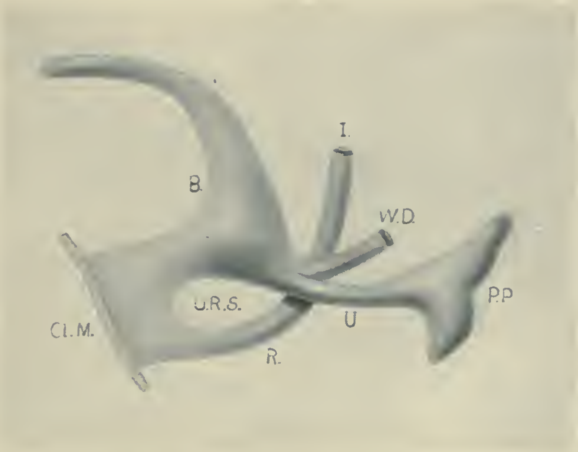
PLATE 8

FIG. 12. From an 11.5 mm. human embryo (× 33). The urorectal septum has almost reached the cloacal membrane. The tip of the ureteral bud has become bulbous, and shows a distinct tendency toward bifurcation. The Wolffian duct and the ureter have acquired separate openings into the bladder side by side. (After model by Keibel.)

FIG. 13. From a 25 mm. human embryo (× 20). The urorectal septum has reached the cloacal membrane, completely dividing the cloaca into bladder and rectum. The dotted line indicates the limit to which the coelom descends, the two layers of this peritoneal pouch later becoming fused to form Denonvilliers' two-layered fascia. The ureter and the Wolffian duct have acquired separate orifices, and the latter has shifted downward and later becomes the ejaculatory duct. (After model by Keibel.)



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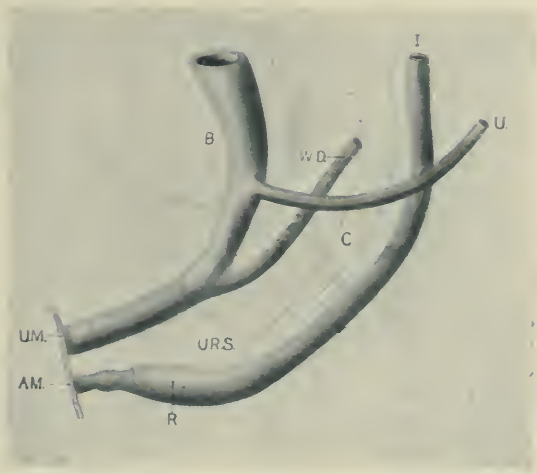

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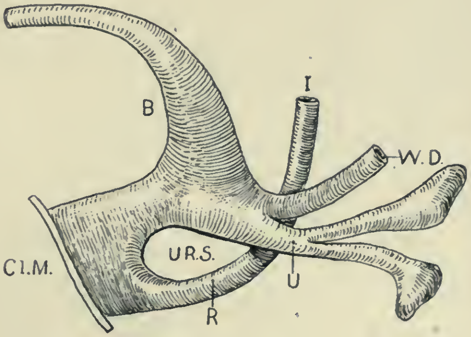
PLATE 9

Fig. 14. Schematic representation of a bifurcation of the primitive pelvis in excess of the normal bifurcation shown in figure 12. It can readily be understood that a dilatation of the lower end of this cleft ureter would produce two separate ureteral orifices in the bladder.

Fig. 15. Cross section through caudal end of a 6 mm. human embryo (× 80), showing both Wolffian ducts entering cloaca and both ureteral buds given off from the Wolffian ducts just at the angle where the latter turn and run cranially. Figure 10 shows how a cross section at this level would cut the Wolffian ducts longitudinally. (Embryo Mall 988, slide 6, row 7, sec. 3.)



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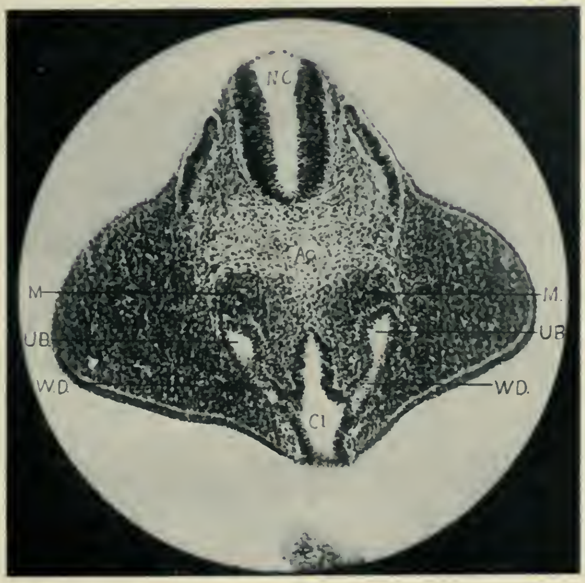

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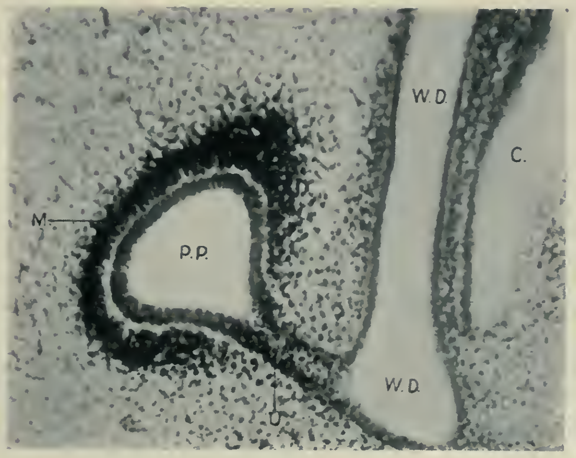
PLATE 10

FIG. 16. Sagittal section through a 7.8 mm. human embryo (× 160), showing in an almost diagrammatic manner the Wolffian duct with its ureteral bud terminating in a bulbous swelling, the primitive pelvis. Surrounding the latter is a zone of metanephrogenic tissue, clearly differentiated from the surrounding mesoderm. (Embryo Mall 1354, slide 5, row 3, sec. 2.)

FIG. 17. Sagittal section through a 6.6 mm. human embryo (× 170), showing another almost diagrammatic picture of the ureteral bud. This section, and the one from which figure 16 was taken, fortunately happened to be in exactly the right plane to cut both Wolffian duct and ureter longitudinally. (Embryo Mall 371, slide 5, row 3, sec. 5.)



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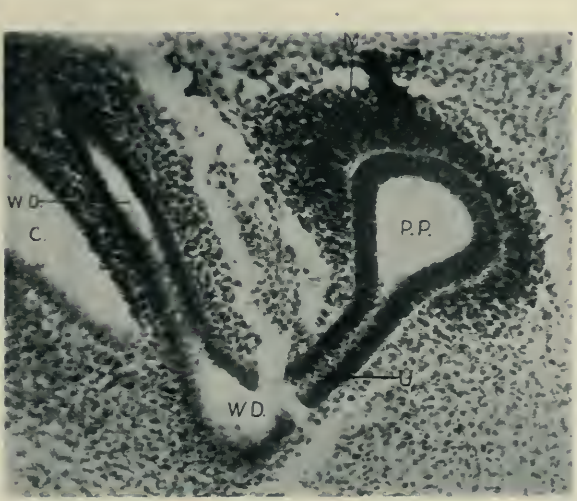

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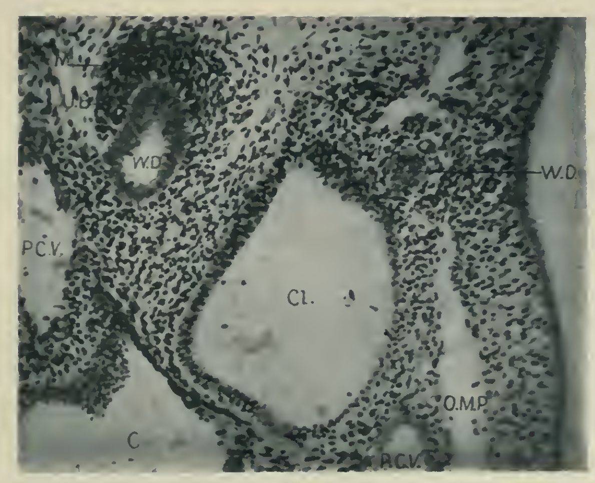
PLATE 11

Fig. 18. Cross section through cloaca and both Wolffian ducts of a 6.5 mm. human embryo (× 170). One Wolffian duct shows a ureteral bud very early in the process of evagination. Note that although the distance which the ureteral tip has grown is less than the diameter of the Wolffian duct, the former is already surmounted by the "cap" of metanephrogenic cells. (Embryo Mall 800, slide 22, row 3, sec. 2.)

Fig. 19. Higher magnification of ureteral bud shown in figure 18 (× 466). Note the sharpness and clearness of the stain of the nuclei of the metanephrogenic cells in contrast with those of the surrounding mesoderm.



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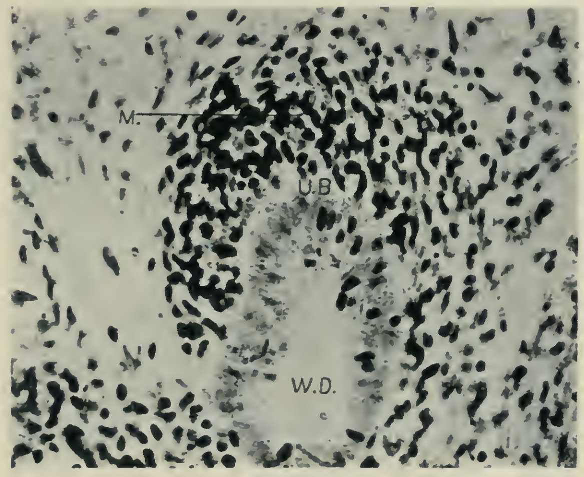

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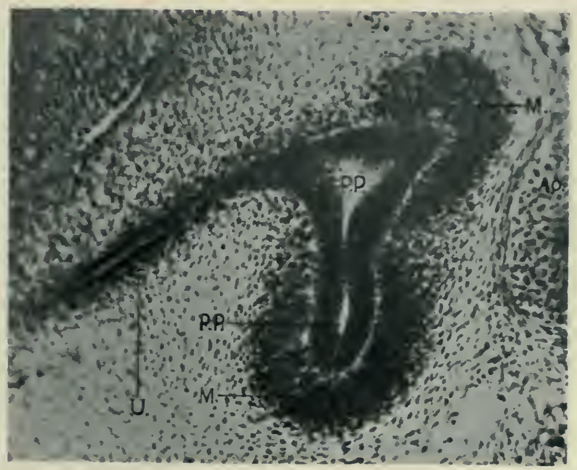
PLATE 12

FIG. 20. Sagittal section through a 10 mm. human embryo (× 170), showing distinct bifurcation of primitive pelvis. This bifurcation may be shown to take place as early as the 8 mm. stage, although it happened that none of the 8 mm. embryos studied were sectioned in the correct plane to demonstrate the bifurcation in a single, clear-cut, diagrammatic picture, as the above section from a 10 mm. embryo supplied. (Embryo Mall 1197, slide 12, row 1, sec. 2.)

FIG. 21. Sagittal section through the cloacal region of a 23 mm. human embryo (× 33), showing cloaca completely separated into urogenital and rectal portion by the urorectal septum. A pouch of peritoneum (c) is seen extending well down beyond the point of entrance of the ejaculatory duct (Wolffian duct) into the future urethra. It is this two-layers of peritoneum that later fuse to form Denonvilliers' fascia. (Embryo Mall 453, slide 24, row 1, sec. 1.)



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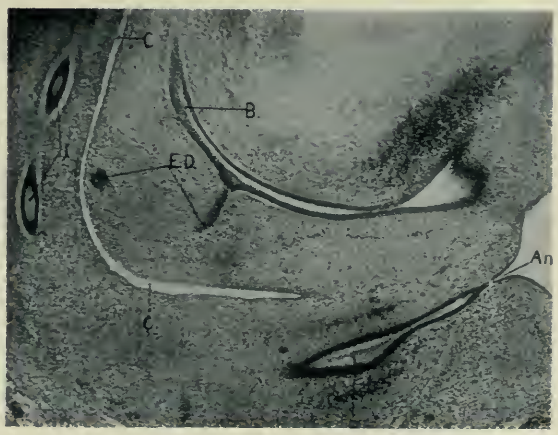

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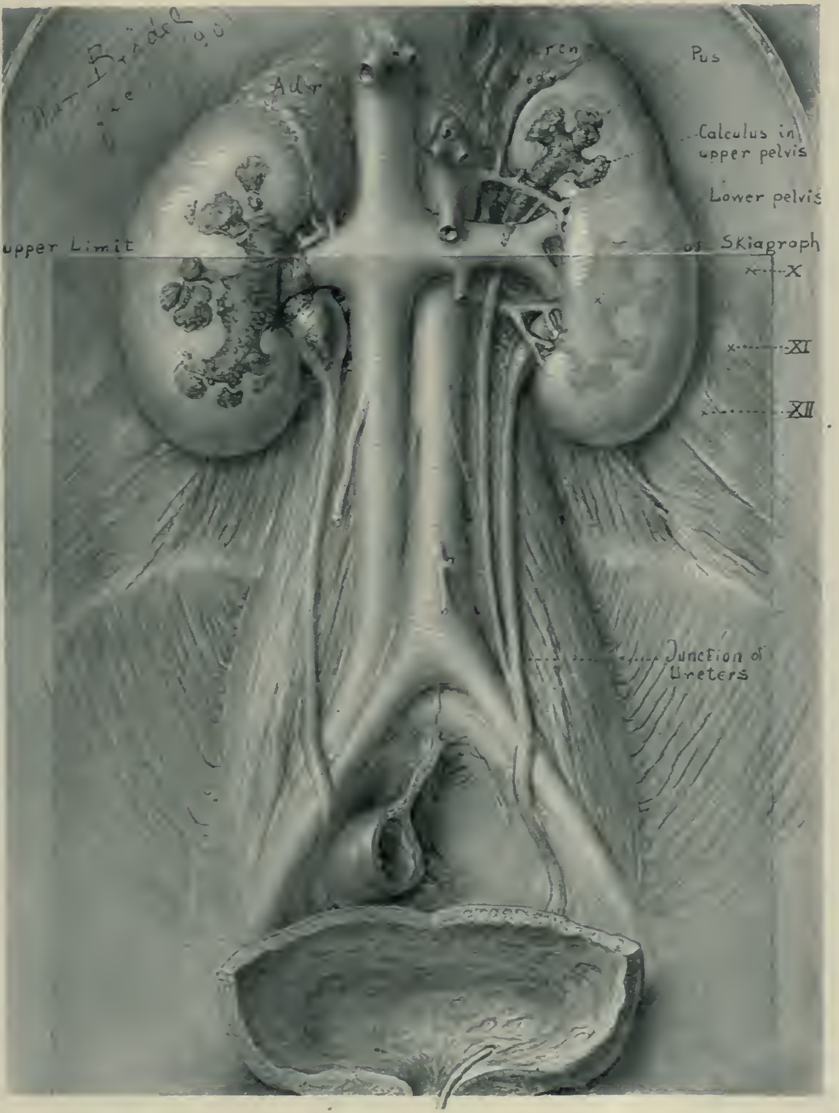
PLATE 13

Fig. 22. Bilateral renal calculi; large branching calculus filling pelvis and calices of right kidney and also the pelvis and calices of the upper portion of the left kidney, which is double. The lower portion of the double kidney is normal. The X-ray plate (as indicated) showed a shadow in the right kidney but none in the left because the plate was placed too low. (Case of H. H. Young.)


Adr
ren
Pus
Calculus in upper pelvis
Lower pelvis
upper Limit of Skiagraph
X
XI
XII
Junction of Ureters

THE BACTERIOLOGY AND MICROSCOPY OF THE CONTENTS OF THE SEMINAL VESICLES POST-MORTEM. A STUDY OF FIFTY-TWO CASES[1]

B. A. THOMAS AND F. G. HARRISON

From the William Pepper Clinical Laboratory, University of Pennsylvania

In view of the unprecedented interest manifested by urologists today in spermatocystitis, and in realization of the focal sepsis occasioned thereby, too little suspected and investigated by the average medical man, be he internist, surgeon or specialist, but nevertheless characterized by a retinue of urinary, arthritic, neurological, mental and even systemic diseases, it behooves the profession to welcome any attempt to study this obscure affection.

This paper is merely the forerunner of a more important one directed to the microscopy and bacteriology of spermatocystitis, during life, as revealed at the time of seminal vesiculotomy. Thus we hope to establish on a firmer basis certain indefinite and conflicting ideas respecting: (1) the presence of spermatozoa in the seminal vesicle, (a) normally and (b) when inflamed; (2) the life or death of spermatozoa in spermatocystitis and (3), the identification of the invading bacteria, gonorrhoeal and non-gonorrhoeal.

Normally, the seminal vesicles elaborate a specific yellowish albuminous secretion, which according to Virchow is a proteid compound, and claimed by Walker to belong to the group of histones. It is insoluble in water, but dissolves readily in acetic acid and a solution of ferrocyanide of potassium; it is not coagulated by heat, unless salts, particularly sodium chloride, are present; liquid when warm, it becomes gelatinous in consistence when cold. Much discussion has prevailed in the past respecting the function of the seminal vesicles, both in the capacity of secretory structures and as reservoirs for semen. The opinion is generally held at present that the spermatocystic secretion is derived from the epithelium of the vesicular mucosa, that it bears a definite though unknown relation to the spermatozoon, and can be differentiated by chemical analysis from the testicular secretion. This view is held by Akutsu, Casper, Fürbringer, Rehfisch, Quinby and many others. In addition to its own peculiar secretion, the seminal vesicle, under normal conditions harbors epithelial cells, occasional leucocytes, lecithin granules, sago bodies and numerous spermatozoa.

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[1] Read before the Philadelphia Pathological Society, January 25, 1917.

Singularly enough there is no unanimity of opinion even today respecting the point as to whether or not the seminal vesicles subserve the function of reservoirs. Hundreds of years ago Fallopius and Regnerus de Sraof contended that the vesicles were containers of semen, while opposed to this view were Wharton van Hornes, Swamerdam and Hunter. The Royal Society of London left the decision with Sraof, but he was unable to form a conclusion on this scientific matter. More recently Rayer states "In the contents of the seminal vesicles there are found some seminal threads, although not so regularly and not so numerously that the seminal vesicles can be considered as storage places for the spermatozoa." Lenhossek and Weisz conclude that the "seminal vesicles positively do not serve as reservoirs for the testicular secretions."

Irrespective of these statements, alleged to be based upon investigations, we believe consensus of opinion favors the belief that the seminal vesicles, in addition to their own secretory function, also serve as reservoirs for the testicular secretion. Evidence to this effect is furnished by the fact that practically all vesicles normally contain varying numbers of spermatozoa, also in our post-morten study of fifty-two cases, many vesicles were found to harbor spermatozoa. Thus the dual function of the vesicles can scarcely longer be contested.

It is not our intention at this time to differentiate the acute, subacute and chronic types, nor to enter into a discussion of the clinical aspects of spermatocystitis. It is sufficient to recall, (1), the frequency of the affection, hence its importance, and (2) the gross pathology associated with the bacteriology. Inflammation of the seminal vesicles may be divisible into the following forms: (1) catarrhal; (2) suppurative, with or without loculations of pus or abscess formation; (3) interstitial and (4) pericystic. On rectal examination, these may vary from an impalpable lesion to a pyovesiculosis of 50 cc. content or a mass the size of a goose egg (Kocher, Petersen). The perivesicular form leading to a chronic infiltration of the trigone and neck of the bladder may lead to symptoms identical with those of prostatism and associated in one of our cases with a residual urine of 15 ounces. In a considerable number of our cases studied post-mortem, atrophy, obliterative changes and inflammatory enlargement of the vesicles were demonstrable.

The frequency of spermatocystitis is yearly becoming more widely recognized, some investigators regarding it as the commonest complication of gonorrhoea (Lloyd, Fuller, Collan, Weisz). It is probably true that epididymitis does not exist without an associated seminal vesiculitis, and the belief is steadily gaining credence that inflammation of the spermatic vesicles is as common, if not more frequent than prostatitis, as a gonorrhoeal complication (Lucas, Colombini, Guépin and Kennedy). Mayer found 60 per cent of patients with posterior urethritis to have involvement of the seminal vesicles. Lewin and Bohm encountered spermatocystitis in 35 per cent and prostatitis in 29 per cent of 1000 gonorrhoeal cases.

Although gonorrhoea is the usual cause of spermatocystitis, it is seldom, in our experience, that the gonococcus can be identified; the vast majority of cases presenting a mixed infection or at least some other superimposed pyogenic bacterium. Post-mortem study in our series failed to demonstrate the gonococcus in a single case. In the living subject, Reich was the first to demonstrate gonococci in a spermatocystic abscess, and v. Sehlen found them in the expressed secretion of the vesicles. Since then this observation has been repeatedly made in 14 to 60 per cent of cases (Collan, Mayer, Möller, Feleki, Finger, Lewin and Bohm). Recognizing the prevalence of spermatocystitis due to gonorrhoea, and conscious of the opinion of some authorities that men who have had repeated attacks of gonorrhoea, invariably are sufferers from chronic inflammation of the seminal vesicles, it should be borne in mind that occasionally other causes are responsible. Among these should be mentioned: (1) bacterial invasion from contiguous structures; (2) urethral instrumentation; (3) circulatory disturbances; (4) systemic infections; (5) perineal trauma according to Kocher and (6) masturbation and venereal excesses. Tuberculosis, an affection of not uncommon occurrence is of such special interest and importance that it deserves separate attention and has been excluded from consideration in this paper.

The content of the inflamed vesicles is a muco-purulent or purulent material mixed with a pellucid filamentous stroma or colloidal brownish liquid containing conglomerated fat globules, desquamated and degenerated epithelial cells, pus, erythrocytes, lecithin granules, concretions, bacteria and possibly spermatozoa. In a case of gonorrhoea complicated by bilateral epididymitis, pyelonephritis and spermatocystitis, Duhot found in the hemorrhagic vesicles a thick, cloudy content consisting of numerous leucocytes and erythrocytes, hematoidin crystals, pigment granules, epithelial cells, extra and intracellular gonococci, a few bacilli, but no spermatozoa. Guelliot and Collan likewise found the inflammatory content devoid of zoösperms. Lewin and Bohm saw either dead or living spermatozoa in 11 per cent of cases; in the remainder none was visible.

The precise bacteriology of the seminal vesicles has always been a matter of much uncertainty and conjecture. There is reasonable ground to doubt the occurrence of a pure gonococcal spermatocystitis, just as there is of a cystitis, prostatis, epididymitis or even a posterior urethritis. The differentiation of the gonococcus from the M. catarrhalis is at times a matter of great difficulty. It will be remembered that although the posterior urethra normally contains no bacteria, the anterior urethra furnishes at least a dozen or fifteen varieties. During the course of a siege of gonorrhoea, invasion of the posterior urethra and its adnexa by the mixed infection from the anterior urethra becomes a simple matter, and then as a rule the gonococcus speedily becomes implanted in the tissues or supplanted by the associated more rapidly growing and virulent pyogenic bacteria. Thus, frequently, the complications and sequellae of gonorrhoea arise.

Huet finds that bacteria may be present in the seminal vesicles of healthy animals, as horses, cattle, pigs and laboratory animals, and attempts to apply his observations to man. He has also found that in animals dying of acute septicemia, the specific organism (anthrax, pneumonia) can be recovered in the vesicular secretions. Furthermore, it was shown definitely that an infection with which the male was suffering could be transmitted to the female during the act of copulation.

Marchildon reports two cases of typhoidal spermatocystitis, that were autopsied and pure cultures of the B. typhosus obtained from both vesicles and prostate.

Fuchs was able microscopically and culturally to demonstrate the B. coli in association with gonococci.

Barney reports a few cases in which sterile cultures were obtained, although in one vesicle the microscopical smear showed a large colony of cocci, possibly diplococci, some of them intracellular. Voelcker reports finding the pneumoccocus in vesicles removed at operation. Picker has repeatedly shown not only this organism but also the gonococcus. Fuller states that in many chronic cases no gonococci can be demonstrated definitely to exist in the urinary tract or in the material expressed from the seminal vesicles; organisms apparently streptococci, however, have been found. Belfield relegates the infection to the colon bacillus and the gonococcus. Schmidt says that the "gonococcus is not the germ which is the one most often found. In the acute stage the gonococcus may pave the way for secondary infection, but it soon becomes extinct and the secondary infectious germs are the cause of the resultant condition and symptoms. In the order of frequency these are the staphylococcus, streptococcus and the colon bacillus. I do not mean, however, that the gonococcus is ever absent in the chronic cases." Smith sums up the evidence and claims that the seminal vesicles are infected "principally by Neisser's diplococcus, and its associates, the staphylococcus, the streptococcus and the colon bacillus."

Squier, in 1913, in spite of negative findings in repeated cultural and bacteriological tests of the vesicular contents, believes in the theory of a mixed infection. In 1915, in view of the multiplicity of results, he forms two conclusions: (1) with the exception of the suppurative cases, the gonococcus is regularly absent; (2) there is almost constant growth of pyogenic bacteria. Referring to the work of Rosenow and Buerger with pneumococci in 1907, he suggests that the gonococcus may undergo a mutation depending upon its environment and declares that "it is not too much to presume that the gonococcus may mutate, and what is in the beginning a Neisserian seminal vesiculitis, is latterly a streptococcic infective process."

From the foregoing diversity of opinion it is apparent that little is definitely known respecting the exact nature of the bacterial flora of spermatocystitis. Moreover many reported bacteriological results have been based upon secretion or material obtained after expression or massage of the seminal vesicles and prostate. Even were it possible by this means to keep the two secretions separate, the method, so far as accurate findings are concerned, is open to serious criticism on account of unavoidable contamination from the bacteria prevalent in the urethra. Absolute indisputable results can be obtained only by incision of the vesicles and direct bacteriological examination of their contents.

Believing that a study of the spermatocystic secretion, postmortem, might be of interest, if not instructive, we submit the following table of fifty-two cases, reserving the more important series, namely those cases studied during life in conjunction with seminal vesiculotomy, for a secondary report.

The cases here tabulated were all autopsied in the Philadelphia General Hospital, and we wish to express our deep appreciation to Dr. Randle C. Rosenberger for his courtesy in placing this material at our disposal. Few, if any, of the bodies were as fresh as might have been desired. Some were seen in a few hours, but many not until after they had been in cold storage for a day or more. In most instances, the bladder with attached seminal vesicles had been removed and placed in a refrigerator for a few to twenty-four or more hours before bacteriological culture was attempted. The age of the subjects ranged from eighteen to seventy-four years. The diagnoses are noted for the respective cases but have no definite significance with respect to the seminal vesicular findings, even in those few cases where a history of gonorrhoea was obtainable, which was the case in only 13.4 per cent, of whom practically one-half showed no growth, and the remainder the colon bacillus, with one exception when the M. albus was isolated; 15.3 per cent denied gonorrhoeal infection, and of these one-fourth demonstrated the colon bacillus. In thirty-seven cases or 71.3 per cent no statement, negatively or positively, of venereal infection was obtainable.

The technique of examination was as follows: The vesicles were sufficiently dissected to expose their exterior. A prominent area of the surface was rendered sterile by searing with a hot blade. The vesicle was then incised with a sterile knife and its lumen and content exposed. Cultures were taken on blood agar or serum, on plain agar and in bouillon. If no growth appeared in two days under the usual cultural conditions, the incubation was continued anaerobically for a few days more. Another portion of the vesicular secretion was then spread on the glass slide, stained and studied microscopically. Finally a hanging drop preparation was made and observed under the microscope.

In sixteen cases B. coli was cultured, but little importance attaches to this, since it was found in a number of subjects who denied venereal infection. Moreover, in view of the high percentage of times this bacterium was cultured as compared with the other organisms, the thought naturally arises, whether this could not have been a post-mortem invasion of the vesicle due to the proximity of the rectum. At any rate the finding supports the belief that intestinal flora may permeate the tissue spaces or minute cellular perforations, and thereby in this manner gain entrance to the urological tract. It is significant, how-

Table of autopsied cases showing microscopical and bacteriological contents of seminal vesicles

NO.	NAME	AGE	DIAGNOSIS	GONORRHOEA DURING LIFE	HANGING DROP	CULTURE	SMEARS MICROSCOPICALLY
1	Brokel	69	Hemiplegia chronic myocarditis		None obtained—vesicles atrophied—lumen could not be found	No culture taken	No fluid could be expressed and no smears made
2	Reaves	28	Pulmonary tuberculosis	–	No spermatozoa seen	No growth	Fluid thick and inspissated, almost gelatinous—no pus cells
3	Featis	51	Acute dilatation heart—chronic myocarditis	–	Well defined and large vesicles — spermatozoa seen	No growth	Spermatozoa
4	Barnes	28	Spinal pachymeningitis	+	Spermatozoa seen	No growth	Spermatozoa
5	Rockmack	60	Senile dementia		Spermatozoa seen	No growth	Spermatozoa
6	Bakas	41	Paresis		Spermatozoa seen	No growth	Spermatozoa
7	Richardson	59	Chronic interstitial nephritis; chronic myocarditis		No spermatozoa	No growth	Very little—practically no fluid in the vesicles—smears = negative
8	Jasper	57	Senile dementia; chronic myocarditis		No spermatozoa	No growth	Negative
9	Nothenius	39	Malignant endocarditis		No spermatozoa	No growth	Few pus cells—no organisms seen—no spermatozoa
10	Hatzfeld	34	Chronic myocarditis paresis		Very thick seminal fluid—no spermatozoa seen	M. aureus	Pus cells—no spermatozoa
11	Fay	60	Diffuse nephritis	–	No spermatozoa	No growth	Negative

12	Prince	46	Pulmonary tuberculosis—left pyopneumothorax		Blood clot in vesicles—no hanging drop	No growth	Red blood corpuscles and a few white blood corpuscles—no spermatozoa seen
13	Marioshelli	65	Bronchiestasis		No spermatozoa	No growth	Negative
14	Keating	47	Pernicious anemia		No hanging drop	No growth	Vesicles atrophied, no lumen found nor fluid expressed, no spermatozoa seen in smears
15	Petrofski	44	Paresis—horse shoe kidney		Spermatozoa seen	B. coli	Few pus cells—spermatozoa
16	Cornery	49	Acute cardia dilatation—chronic nephritis—alcoholism	+ Also syphilis	Spermatozoa seen	No growth	Spermatozoa
17	Bond	50	Pyothorax—myocarditis		Spermatozoa seen	B. coli	Spermatozoa—pus cells—epithelial cells
18	Dean	18	Miliary tuberculosis—tuberculosis meningitis		Spermatozoa seen	No growth	Few pus cells—spermatozoa
19	Weikle	53	Tabes—aortic regurgitation myocarditis		Spermatozoa seen	No growth	Spermatozoa
20	Monaghan	63	Aneurism — nephritis — emphysema — pneumothorax	+ Also syphilis	Spermatozoa seen	B. coli	Spermatozoa—pus cells
21	McGonigle	56	Epilepsy — pulmonary tuberculosis—chronic interstitial nephritis	+	No spermatozoa—left testicle absent—old healed scar over scrotum—right testicle O. K.	B. coli	Pus in prostate—pus in smears—no spermatozoa

Table of autopsied cases—continued

NO.	NAME	AGE	DIAGNOSIS	GONORRHOEA DURING LIFE	HANGING DROP	CULTURE	SMEARS MICROSCOPICALLY
22	Vloerburg	57	Tabes—paresis		No spermatozoa	No growth	No pus cells—no spermatozoa
23	McClain	28	Pneumonia		No spermatozoa	M. aureus	Few pus cells—no spermatozoa
24	McNama	43	Granuloma—fungoides	—	No spermatozoa	No growth	Large and well defined vesicles—no pus cells—no spermatozoa
25	Monocelli	46	Cerebro-spinal lues—hemiplegia		No spermatozoa	B. coli	Pus cells—no spermatozoa
26	Williams	26	Lobar pneumonia		No spermatozoa	No growth	Negative
27	Wagner	74	Hemiplegia—senile broncho-pneumonia		Hypertrophy of prostate — vesicles atrophied — no spermatozoa	B. coli	Only small amount of fluid—few pus cells—no spermatozoa
28	Bryant	50	Intra-cranial hemorrhage	—	No spermatozoa	No growth	Negative
29	Printz	42	Cerebral lues—hypostatic pneumonia		Spermatozoa seen	B. coli	Few pus cells—spermatozoa
30	Howard	30	Chronic interstitial nephritis		Spermatozoa seen	No growth	Negative
31	Buggey	61	Cerebral thrombosis		No spermatozoa	No growth	Negative
32	Maloney	50	Myocarditis — hemiplegia		No spermatozoa	B. coli	Few pus cells—no spermatozoa
33	Shaw	59	Paresis—myocarditis		No spermatozoa	No growth	Negative
34	Prendergast	50	Chronic endocarditis—anemia—cirrhosis of liver		No spermatozoa	No growth	Negative

35	DeSondro	49	Perforation intestinal typhoid fever		No spermatozoa	No growth	Negative
36	Banks	42	Aneurism of thoracic aorta	+ Also syphilis	Spermatozoa seen	No growth	Spermatozoa
37	Harris	56	Myocarditis—nephritis hypertrophic prostate	—	Thrombosis in left seminal vesicle — right shows spermatozoa	No growth	Few pus cells—spermatozoa with tails off and broken
38	Erickson	50	Myocarditis—diabetes nephritis		Very thick and inspissated seminal fluid—no spermatozoa	B. coli	No pus cells—negative
39	Fagen	44	Pulmonary tuberculosis		Vesicles well defined—large lumen — no spermatozoa	B. coli	No pus cells—no spermatozoa
40	Dempsey	46	Paraplegia —bronchopneumonia — mitral disease		No spermatozoa	No growth	Crystals—triple phosphates—very little fluid in vesicles—no pus cel's
41	Wharton	37	Chronic myocarditis		Well defined vesicles—spermatozoa seen	B. coli	No pus cells seen—spermatozoa
42	Bowen	44	Chronic myocarditis		Not much fluid present—few spermatozoa	No growth	Red blood corpuscles and white blood corpuscles—few spermatozoa
43	Komszey	64	Lobar pneumonia		Vesicles and prostate atrophied—no lumen of vesicles found—no hanging drop	No culture taken	No pus cells—spermamatozoa seen
44	Welsh	44	Aortic regurgitation—mitral regurgitation—hydrothorax	+	Well defined vesicles—spermatozoa seen	M. albus	No pus cells—spermatozoa seen

Table of autopsied cases—concluded

NO.	NAME	AGE	DIAGNOSIS	GONORRHOEA DURING LIFE	HANGING DROP	CULTURE	SMEARS MICROSCOPICALLY
45	Steventon	47	Delirium tremens—lobar pneumonia	–	Spermatozoa seen	B. coli	No pus cells—spermatozoa seen
46	Conway	28	Myocarditis — morphine and heroin habitué		Gelatinous substance in vesicles and practically no fluid—no spermatozoa seen	B. coli	Few pus cells—no spermatozoa — mucoid substance
47	Fuchs	59	Myocarditis — choelethiasis — esophageal obstruction		Very ittle fluid in vesicles—few spermatozoa	No growth	Spermatozoa
48	Chester	66	Senile dementia — chronic nephritis		Very little fluid—no spermatozoa seen	B. coli	Crystals—triple phosphates—no pus cells —no spermatozoa—red blood corpuscles
49	Ball	54	Transverse myelitis—cystitis—pyelitis	+ Also syphilis	Very little fluid in vesicles—no spermatozoa	B. coli	Crystals—no pus cells —no spermatozoa
50	Powell	31	Pulmonary tuberculosis—hypomania		Many spermatozoa	No growth	Occasional pus cells—many spermatozoa
51	Long	49	Pulmonary tuberculosis—tertiary lues	–	Very like inspissated fluid in vesicles—no spermatozoa	B. coli	Pus cells—crystals—no spermatozoa
52	Michael	44	Broncho-pneumonia—pulmonary tuberculosis—appendicitis		Spermatozoa seen	No growth	Spermatozoa—no pus cells

ever, that in all save six cases of colon infection, pus cells were demonstrable in the vesicular secretion, evidencing the probability of an ante-mortem spermatocystitis due to this bacterium.

In two cases, one of myocarditis and paresis, the other of pneumonia, M. aureus was found in association with pus cells in the vesicles.

In one case with a history of gonorrhoea, M. albus was cultured.

In a few cases B. subtilis was obtained in the culture. This was undoubtedly the result of contamination.

The high percentage of sterile cultures is not surprising, when it is realized that the subjects and vesicles were refrigerated for considerable periods previous to the time of taking cultures, and helps to explain the failure to obtain any bacterial growth in a number of cases presenting pus in the vesicles.

A review of the tabulated cases reveals the fact that in twenty-one or over 40 per cent, spermatozoa occurred in the presence of evidence of inflammation, either bacteria or pus or both. Obviously, the zoösperms were all dead. In fourteen cases exhibiting signs of spermatocystitis, or approximately 27 per cent, no spermatozoa were discoverable.

CONCLUSIONS

1. The seminal vesicles harbor spermatozoa after death, and therefore presumably during life.
2. This function is exercised in the presence of inflammation (spermatocystitis), although in a large percentage of inflammatory cases no spermatozoa can be found (post-mortem).
3. The determination of the viability of the zoösperm in the presence of seminal vesiculitis, the exact identification, classification and relative frequency of the invading bacteria, particularly with reference to gonorrhoea, are questions impossible of solution by post-mortem investigation, and will constitute a secondary and final report after bacteriological and microscopical study conducted in conjunction with seminal vesiculotomy on the living subject.

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THE RELATION OF THE NON-PROTEIN NITROGEN TO THE UREA NITROGEN OF THE BLOOD

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Many of the observations dealing with the relation of the non-protein nitrogen to the urea nitrogen of the blood were obtained several years ago by methods which did not yield results strictly comparable with those of today. Hence, additional data on this subject have a considerable degree of interest, particularly in the study of diseases associated with renal insufficiency.

The micro-methods, as employed at present for the determination of urea, are much more rapid and easier of manipulation than those for non-protein nitrogen of the blood. The question, therefore, constantly arises: will the urea nitrogen of the blood yield data whereby the presence or absence of retention of waste products may be adequately judged, or must the total non-protein nitrogen be determined as well?

The methods employed in this investigation were the procedure of Folin and Denis (1) for the non-protein nitrogen and that of Marshall (2) for the urea nitrogen in the blood. The material studied in the present series consists of 306 observations on 165 patients. In order to save space and render the conclusions clearer, only a few of these are discussed in detail; the majority are summarized in the tables. The upper normal limit of non-protein nitrogen has been regarded as 30 mgm. per 100 cc. of blood, that for urea nitrogen as 15, for reasons set forth a short time ago (3), and the tabulations have been made on this basis.

The value given for the non-protein nitrogen of the blood varies much with the method employed in its determination. The different coagulants used to separate the protein from the non-protein part of the blood evidently precipitate unequal fractions. Thus, the trichloracetic method of Greenwald (4) yields considerably higher results for the non-protein nitrogen than the methyl alcohol method of Folin. This is confirmed by our experience. Much of the acetone-free methyl alcohol obtained during the last four years has been unsatisfactory in that it contained a considerable amount of nitrogen and because it did not precipitate a constant nitrogenous fraction as protein. Hence, ethyl alcohol was used and yielded good results, provided the alcohol-blood mixture was allowed to stand twenty-four hours before filtering. Under these circumstances, the figures for non-protein nitrogen were duplicates of those obtained with the satisfactory grades of methyl alcohol. The results of non-protein nitrogen determinations of the blood are therefore comparable when similar methods are employed; if compared with other data, due allowance must be made for possible differences in the chemical procedures. All the cases studied are summarized in table 1.

TABLE 1

Percentage of total non-protein nitrogen of the blood existing as urea nitrogen in all cases examined

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	101 +
0–40	20	0	0	0	0	0	0	0	0
41–50	32	5	2	2	0	0	0	0	1
51–60	37	12	3	0	3	0	0	1	2
61–70	29	8	4	5	0	2	1	3	8
71–80	13	12	4	4	4	4	4	2	27
81–90	1	5	1	1	2	6	2	2	24
91+	1	1	0	0	1	0	1	0	4
Total number of observations	133	43	14	12	10	12	8	8	66
Average per cent urea N of total non-protein nitrogen.	54.9	65.7	64.3	66.7	73.0	78.3	78.8	71.2	77.6

* In this as well as the similarly designed subsequent tables, the scale at the top represents the milligrams of non-protein nitrogen per 100 cc. of blood; the scale at the left the percentage of urea nitrogen of the total non-protein nitrogen; the inserted figures the number of determinations falling in each group.

From table 1 it is apparent that as the non-protein nitrogen of the blood rises it is accompanied by a disproportionately rapid increase in the urea. This is expressed in the upward trend of the percentage figures for the urea nitrogen of the total non-protein nitrogen. This finding bears out the observations of Farr and Austin (5), Tileston and Comfort (6), as well as of authors working with other methods, notably Hohlweg (7) and Obermeyer and Popper (8). Woods (9), on the other hand, reports that the urea nitrogen in cases of chronic nephritis, whether the non-protein nitrogen of the blood be high or low, maintains roughly the same concentration of 63.4 per cent. In the present observations this is true neither of the cases taken as a whole (table 1) nor of the instances of chronic nephritis (table 3).

TABLE 2

Approximate percentages of urea N as total non-protein nitrogen increases in the blood

TOTAL NON-PROTEIN NITROGEN	APPROXIMATE UREA N
Mgm. per 100 cc. blood	*Percentage of total non-protein nitrogen*
0–30	55
31–60	65
61+	75

From table 1 it is possible to construct an approximate guide for estimating the non-protein nitrogen from the urea nitrogen, and *vice versa,* when only one of the two determinations is available. Such a scale is shown in table 2.

The material has been subdivided as follows for more detailed tabulation:

1. Chronic nephritis, not including the cases complicated by myocardial insufficiency or uremia (table 3).
2. Nephritis, complicated by uremia (table 4).
3. Myocardial insufficiency, not associated with nephritis (table 5).
4. Chronic nephritis, associated with myocardial insufficiency (table 6).
5. Acute nephritis (table 7).

6. Cases with a high non-protein nitrogen in the blood, but not suffering with nephritis or myocardial insufficiency. (This group included cases of polycystic kidney, bichloride of mercury poisoning, tabes dorsalis, diabetes mellitus, amyloidosis and hypertrophied prostate.)

TABLE 3

Cases of chronic nephritis, not including those complicated by myocardial insufficiency or uremia

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	101 +
0–40	7	0	1	0	0	0	0	0	0
41–50	15	2	1	3	0	0	0	0	0
51–60	15	9	1	0	3	0	0	0	0
61–70	13	3	2	1	0	2	0	2	2
71–80	3	6	3	2	3	1	2	0	4
81–90	0	4	0	1	1	4	0	0	1
91–100	0	0	0	0	0	0	0	0	2
Total number of observations....................	53	24	8	7	7	7	2	2	9
Average per cent urea N of total non-protein nitrogen.	53.8	65.4	61.9	62.1	67.9	77.9	75.0	65.0	78.3

TABLE 4

Cases of nephritis complicated by uremia

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	101 +
0–40	0	0	0	0	0	0	0	0	0
41–50	0	0	0	0	0	0	0	0	0
51–60	0	0	0	0	0	0	0	0	1
61–70	0	0	0	0	0	0	0	1	3
71–80	2	2	0	0	0	0	1	1	12
81–90	0	2	0	0	0	1	0	1	12
91–100	0	0	0	0	0	1	1	0	1
Total number of observations....................	2	4	0	0	0	2	2	3	29
Average per cent urea N of total non-protein nitrogen.	75.0	80.0				90.0	85.0	75.0	78.1

The conclusions which may be drawn from these statistics are as follows:

TABLE 5

Cases of myocardial insufficiency not complicated by nephritis

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	101 +
0–40	0	0	0	0	0	0	0	0	0
41–50	2	0	0	0	0	0	0	0	0
51–60	6	0	0	0	0	0	0	0	0
61–70	4	0	0	0	0	0	0	0	0
71–80	2	1	0	0	0	0	0	0	0
81–90	0	1	0	0	0	0	0	0	0
91–100	0	0	0	0	0	0	0	0	0
Total number of observations	14	2	0	0	0	0	0	0	0
Average per cent urea N of total non-protein nitrogen	59.3	80.0							

TABLE 6

Cases of chronic nephritis complicated by myocardial insufficiency

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	101 +
0–40	1	0	0	0	0	0	0	0	0
41–50	2	1	1	0	0	0	0	0	0
51–60	4	0	0	0	0	0	0	0	0
61–70	1	3	0	1	0	0	0	0	0
71–80	1	2	0	0	0	0	0	0	0
81–90	1	0	0	0	0	0	1	0	1
91–100	1	0	0	0	1	0	0	0	1
Total number of observations	11	6	1	1	1	0	1	0	2
Average per cent urea N of total non-protein nitrogen	64.5	65.0	45.0	65.0	95.0		85.0		90.0

In chronic nephritis, not complicated by myocardial insufficiency or uremia, the relation of the urea nitrogen to the total non-protein nitrogen of the blood shows that the urea increases faster than the non-protein nitrogen, the increase being very similar to that which is found when all the cases are averaged (table 1), and presenting no special characteristics.

In cases of nephritis complicated by uremia, the percentage of urea nitrogen has a tendency to be higher than in any other class of cases. Especially noteworthy is the value of 75 to 80 per cent in instances in which the non-protein nitrogen of the blood is 40 mgm. per 100 cc. or less.

TABLE 7

Cases of acute nephritis

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD								
	0–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	101 +
0–40	1	0	0	0	0	0	0	0	0
41–50	3	0	0	0	0	0	0	0	0
51–60	2	0	1	0	0	0	0	0	0
61–70	2	1	1	1	0	0	0	0	0
71–80	2	1	0	2	0	0	1	0	1
81–90	0	0	0	0	0	1	0	0	3
91–100	0	1	0	0	0	1	0	0	0
Total number of observations......................	10	3	2	3	0	2	1	0	4
Average per cent urea N of total non-protein nitrogen.	56.5	78.3	60.0	71.7		90.0	75.0		82.5

TABLE 8

Cases with high total non-protein nitrogen in blood, not included in previous groups

UREA N PER CENT OF TOTAL NON-PROTEIN NITROGEN	MILLIGRAMS OF NON-PROTEIN NITROGEN PER 100 CC. BLOOD						
	41–50	51–60	61–70	71–80	81–90	91–100	101 +
0–40	0	0	0	0	0	0	0
41–50	0	1	0	0	0	0	0
51–60	1	0	0	0	0	1	0
61–70	0	1	0	0	1	0	1
71–80	0	0	1	2	2	1	2
81–90	0	0	1	0	1	0	4
91–100	0	0	0	0	0	0	1
Total number of observations....	1	2	2	2	4	2	8
Average per cent urea N of total non-protein nitrogen...........	55.0	55.0	80.0	75.0	75.0	65.0	81.3

Cases of myocardial insufficiency show a marked rise in the percentage of urea nitrogen in those rather rare instances when the non-protein nitrogen increases in the blood beyond the normal of 30 mgm. per 100 cc.

Patients suffering with chronic nephritis complicated by myocardial insufficiency accumulate urea more rapidly in proportion to the other non-protein nitrogenous constituents of the blood than do the cases of chronic nephritis not associated with myocardial insufficiency.

Cases with acute nephritis exhibit a decidedly higher percentage of urea nitrogen than do the instances of chronic nephritis.

The cases with a high non-protein nitrogen in the blood, not included in the previous groups, have a lower proportion of urea nitrogen to the total non-protein nitrogen of the blood than those afflicted with uremia, and they approximate the figures given for chronic nephritis.

These general conclusions require a close analysis before they can be utilized in clinical medicine or to point the way towards the solution of many problems in pathological physiology and chemistry. The present observations call for but few comments.

The cases with the normal total non-protein nitrogen of the blood—that is, less than 30 mgm. per 100 cc., show a higher proportion of urea nitrogen than the normal of 50 per cent. This finding has been frequently commented on since Folin and Denis (10) demonstrated that even cases without apparent renal involvement exhibited this phenomenon.

Recently, Slemons and Morriss (11) furnished very striking proof of this observation. These investigators found that during pregnancy, with the occurrence of complications not necessarily related to renal impairment (psychosis, obstetrical operations, cardiac lesions, and still-born infants), the percentage of urea nitrogen was considerably raised in the mother and the fetus as well, although the total non-protein nitrogen of the blood remained within the normal range.

The average of 54.9 per cent in the present series is not very far above the normal of 50 per cent. In every class of cases except in that of the uremics charted in this series, there are many instances in which the urea percentage of the total non-protein nitrogen is less than 50. Taking these facts into consideration, it becomes a question of extreme interest to establish the exact relation of these figures to uremia. From the present data it would seem that every case of uremia exhibiting a low total non-protein nitrogen in the blood revealed an abnormally high percentage of urea nitrogen, while the reverse, that every case with normal total non-protein nitrogen with a high percentage of urea nitrogen had a tendency to uremia certainly was not true. The observations covering this point in the course of uremia are very few. However, such cases are rarities, and it is the scarcity of material in this field that has prevented the accumulation of more data. All cases with normal total non-protein nitrogen of the blood and a comparatively high percent age of urea nitrogen (70 per cent or over) are presented in table 9. Except for the possible fact that uremia does not

TABLE 9

All cases exhibiting a high percentage (70 per cent or higher) of urea nitrogen, the total non-protein nitrogen being within normal limits, that is, 30 mgm. per 100 cc. or less

	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN
	Total Non-Protein Nitrogen	Urea N	
Chronic nephritis	23	16	70
Chronic nephritis	27	19	71
Uremia	24	17	71
Lobar pneumonia	24	17	71
Pyelitis	24	17	71
Chronic nephritis	30	22	73
Uremia	23	17	74
Chronic nephritis	23	17	74
Myocardial insufficiency	27	20	74
Myocardial insufficiency	24	18	75
Chronic nephritis	21	16	76
Acute nephritis	25	19	76
Tabes dorsalis	29	23	79
Chronic nephritis and myocardial insufficiency	23	19	83
Chronic nephritis and myocardial insufficiency	22	20	91

occur when the urea nitrogen is less than 70 per cent of the total non-protein nitrogen, the high values of urea nitrogen, while the total non-protein nitrogen is within normal limits, do not furnish data of diagnostic value.

In acute renal disease, followed by improvement, the percentage of urea nitrogen in the blood may rise and again return to the normal of 50 per cent or less, thus reflecting the progress of the condition. One case of this sort is cited in table 10. There is one point demanding emphasis seen in this and many similar cases: the high percentage of the urea nitrogen is not necessarily associated with the accumulation of these substances in the blood, but will be present even when they are normal in quantity. Thus, in the present instance (table 10), on December 6, 8 and 13, while the total non-protein nitrogen is distinctly within normal limits, the percentage of the urea nitrogen is 63, 64 and 56, and only reaches the normal of less than 50 per cent (44 per cent in this observation) a week later, when convalescence is almost complete. To a certain extent, therefore, the increased percentage of urea nitrogen may be regarded as a sign of renal insufficiency, even when the total non-protein nitrogen is within normal limits.

TABLE 10

Data from a case of acute nephritis, demonstrating the change from a high to a normal percentage of urea nitrogen during convalescence. Med. No. 34901. Male, age 25. Acute nephritis, recovering almost completely within the period covered by the observations

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN
	Total non-protein nitrogen	Urea N	
October 27	60	45	75
November 1	57	36	63
November 3	49	27	55
November 30	32	22	69
December 6	19	12	63
December 8	14	9	64
December 13	16	9	56
December 20	18	8	44

The relation of the urea nitrogen to the total non-protein nitrogen exhibits a tendency to remain unchanged in each patient. Thus, three cases of chronic nephritis over considerable periods showed a fairly constant concentration of urea nitrogen at a normal level (table 11), at a level of 65 per cent (table 12) and at 70 to 80 per cent respectively (table 13). This moderate fixation is not to be accounted for by unvarying values of the total non-protein nitrogen, for in each patient these fluctuated widely. It is exceedingly difficult to determine in what function or functions this regulation lies. The protein katabolism and anabolism may result in exceedingly marked loss or retention of nitrogen, which at times may be reflected in the level of the total non-protein nitrogen and urea nitrogen of the blood, at others, not; in spite of this, the percentage of urea nitrogen remains fairly constant (tables 12 and 13). Myers and Lough (12) have shown how the kidney, as its efficiency becomes diminished, has a progressive, selective action in its inability to excrete the various non-protein nitrogenous constituents found in the urine. This probably plays a very great rôle in influencing the percentage composition of the various non-protein nitrogenous components of the blood.

It is tempting to assume that the metabolic activities of the tissues through increased protein breakdown may also be responsible for part of the picture. However, when cases are examined in which there is retention of nitrogen due to renal insufficiency alone, not complicated by changes in the other tissues of the body, the same high percentage of urea nitrogen is demonstrated. Polycystic disease of the kidney represents such a condition. A case of this kind was studied through the courtesy of Dr. L. F. Barker, and was found to have the same increase in the percentage of the urea nitrogen in the blood as the instances of nephritis.

When anuria is present and when the non-protein nitrogenous products are retained in their entirety, there is an almost immediate rise in the percentage of the urea nitrogen of the total non-protein nitrogen of the blood. This may be noted in the dog experiment (table 15) and in the case of bichloride poison-

TABLE 11

Data from a case of chronic nephritis exhibiting an increased total non-protein nitrogen in the blood until a very low protein diet was resorted to. The percentage of urea N wilh one exception within normal limits. Med. No. 34543. Male, age 35

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN
	Total non-protein nitrogen	Urea N	
November 13	59	23	39
November 15	62	26	42
November 21	22	12	55
November 29	24	12	50
December 7	14	5	36
December 12	16	8	50

TABLE 12*

Data from a case of chronic nephritis with a fairly constant percentage of the urea N (about 65). The absolute quantity of the total non-protein nitrogen and urea N of the blood, as well as their relative proportions, bear little relation to the retention or loss of nitrogen to the body as a whole

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN	N GRAMS PER DAY FOR INTERVAL BETWEEN BLOOD DETERMINATIONS					N GRAMS BALANCE FOR WHOLE PERIOD
	Total non-protein nitrogen	Urea N		Urine	Feces	Output	Intake	Balance	
January 14	36	23	64						
February 8	50	33	66	13.37	1.00†	14.37	12.50	−1.87	−46.75
February 18	32	22	69	12.14	0.90	13.04	13.52	+0.48	+ 4.80
February 22	30	20	67	9.10	1.03	10.13	13.26	+3.13	+12.52
March 5	29	18	62	16.02	1.50	17.52	16.17	−1.35	−14.85
March 17	26	15	58	19.34	1.87	21.21	17.74	−3.47	−41.64

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* The methods employed in obtaining the data in tables 12 and 13 were the Kjeldahl procedure for the nitrogen values in the urine and feces and the tables of Atwater and Bryant to determine the protein and nitrogen content of the foods: United States Dept. of Agriculture, Bulletin No. 28 (Revised Edition), 1906.

† Nitrogen content of feces estimated in this period.

TABLE 13

Data from a case of chronic nephritis with a fairly constant percentage, of 70–80 of the urea N regardless of whether the total non-protein nitrogen is high or low. The absolute quantity of total non-protein nitrogen and urea N of the blood, as well as their relative proportions, do not bear a constant relation to the retention or loss of nitrogen to the body as a whole. Med. No. 34557. Male, age 25

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN	N GRAMS PER DAY FOR INTERVAL BETWEEN BLOOD DETERMINATIONS					N GRAMS BALANCE FOR WHOLE PERIOD
	Total non-protein nitrogen	Urea N		Urine	Feces	Output	Intake	Balance	
October 8.....	125	99	79						
October 14.....	145	126	87	2.76	0.89	3.65	1.02	−2.63	−15.78
October 21.....	123	103	84	5.00	0.71	5.71	1.49	−4.22	−29.54
October 29.....	66	49	74	5.56	0.62	6.18	2.04	−4.14	−33.12
November 16.....	95	63	66	3.84	1.00	4.84	6.31	+1.47	+26.46
November 23.....	79	55	70	4.45	0.36	4.81	7.25	+2.44	+17.08
November 31.....	41	30	73	3.59	0.85	4.44	2.58	−1.86	−13.02
December 6.....	32	23	72	3.09	0.97	4.06	2.83	−1.23	− 7.38
December 10.....	36	26	72	2.86	0.56	3.42	4.18	−0.76	− 3.04
January 12.....	68	52	76	2.77	0.80	3.57	4.27	−0.70	−23.10
January 25.....	63	45	71	3.18	0.85	4.03	3.03	−1.00	−13.00
February 19.....	194	153	79	1.96	1.03	2.99	3.93	+0.94	+23.50
February 23.....	192	149	78	3.17	2.98	6.15	2.79	−3.36	−13.44
March 3.....	216	170	79	3.52	2.80	6.32	5.79	−0.53	− 4.77
March 9.....	205	161	79	2.99	4.39	7.38	5.76	−1.62	− 9.72
March 10.....	210	174	83	2.64	3.39	6.03	5.89	−0.14	− 0.14
March 11.....	212	175	83	1.99	3.90	5.89	6.29	+0.40	+ 0.40
March 15.....	210	168	80	0.66	3.69	4.35	7.50	+3.15	+12.60
March 19.....	196	144	74	1.05	2.50	3.55	5.01	+1.46	+ 5.84
March 20.....	210	168	80	0.92	1.51	2.43	7.09	+4.66	+ 4.66
March 21.....	222	175	79	died					

ing reported by Lewis and Rivers (13) from this laboratory. The same methods were employed in the observations of these authors, hence, their figures are comparable to those reported in the present series. They found that as the non-protein nitrogenous products accumulated in the blood, the urea nitrogen increased more rapidly than the remainder. The percentage of urea nitrogen reached the level of 83 per cent and gradually returned to a normal of 50 per cent or less as the kidneys recovered. In this instance, as Lewis and Rivers indicate, tissue destruction may have an influence, though a minor one. After nephrectomy in the dog, which may be regarded as an example of maximal uncomplicated renal insufficiency, the percentage of urea nitrogen rapidly rose as high as 86 per cent, and remained in this neighborhood until death supervened.

Taking these facts into consideration, it would seem that ordinarily when protein material is metabolized, approximately 80 per cent of the nitrogen passes into the blood in the form of urea, which is the percentage of urea nitrogen found in the normal urine. Kidneys whose function is not involved maintain the percentage of urea nitrogen of the total non-protein nitrogen at a level of 50 per cent or less in the blood. As the

TABLE 14

Data from a case of congenital polycystic kidneys. There is a high percentage of urea N in this patient, who may be considered to exhibit a type of renal insufficiency not complicated by abnormal metabolic conditions in other tissues. Med. No. 33441. Male, age 43

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN
	Total non-protein nitrogen	Urea N	
February 6	86	70	81
February 10	112	90	80
February 19	86	69	80
March 2	88	62	70

TABLE 15

Data from a nephrectomized dog. The percentage of the urea N rapidly rises

DATE	MILLIGRAMS PER 100 CC. BLOOD		PER CENT UREA N OF TOTAL NON-PROTEIN NITROGEN	REMARKS
	Total non-protein nitrogen	Urea N		
December 6	23	10	44	Blood obtained at time of nephrectomy
December 7	78	54	69	
December 8	138	119	86	
December 9	205	166	81	
December 10	275	232	84	Died

kidneys become inefficient, their impairment of function is recorded in a rise of the percentage of urea nitrogen.

CONCLUSIONS

1. The body usually metabolizes protein in such a manner that approximately 80 per cent of the nitrogen set free in the blood is in the form of urea. The selective action of the kidney maintains the urea nitrogen at a level of 50 per cent or less of the total non-protein nitrogen of the blood. An impairment of renal function, even of very slight degree, may result in an increase of the percentage of urea nitrogen.

2. The increased percentage of urea nitrogen may occur whether the total non-protein nitrogen is high or low.

3. Cases with acute renal conditions show a high percentage of the total non-protein nitrogen as urea nitrogen of the blood, which returns to normal as convalescence occurs.

4. Individual patients whose clinical condition does not vary appreciably exhibit a constant percentage of urea nitrogen, whether the total non-protein nitrogen be high or low.

5. From the clinical point of view, figures for urea nitrogen are preferable to those for total non-protein nitrogen because:

a. The method for urea nitrogen of the blood is simpler.

b. The methods for urea nitrogen are perfected so that they yield constant results which are comparable to those of other observers, while this is not true of the various means of determining the total non-protein nitrogen of the blood.

6. The percentage of the non-protein nitrogen occurring as urea nitrogen, as well as the other non-protein nitrogenous fractions in the blood, while apparently of considerable importance, requires much more detailed study if it is to be of any great clinical significance in the future. (This does not refer to the absolute quantities of many of these constituents, notably urea, creatinine and uric acid, which are better understood and have proved to be of value as guides to the clinician.)

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THE ADVANTAGE OF PYELOTOMY DRAINAGE FOR NEPHROTOMY WOUNDS

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A tradition has been handed down from the early days of kidney surgery warning us that incisions of the kidney pelvis heal badly. This tradition doubtless had its origin in the slow healing or permanent fistulae resulting from simple drainage of the widely distended pelvis of a hydronephrotic kidney. During the past decade we have learned that the kidney pelvis heals fully as well as the kidney parenchyma if there is no obstacle to the outflow of urine. With ureter and urethra free a wound, whether in pelvis or parenchyma, is calculated to heal quite promptly. There seems little need of protecting the wound in the kidney pelvis by wrapping it with perirenal fat, indeed one sometimes even doubts the necessity of suture, for unsutured wounds of the pelvis seem to heal almost as quickly as do those that are carefully sutured, on the condition always that the lower urinary passages are free.

On the other hand, it has been my misfortune to note unexpectedly slow healing in a number of nephrotomy wounds. These have sometimes continued to discharge urine two or three weeks or more, even when there was no very evident obstruction to the outflow of urine. In such cases the indwelling ureter catheter, or even the simple passage of the ureter catheter for irrigation of the kidney pelvis, has usually sufficed to expedite the healing. Yet I do not at present recall any slow healing pyelotomy wounds, though it has been my custom to do nothing to expedite the healing of these wounds.

It is further to be noted that various surgeons have made attempts to keep the upper end of the ureter patent after certain operations upon the kidney or its pelvis. Thus Albarran long ago introduced the indwelling catheter for this purpose, and Peck has suggested the insertion into the upper ureter of a catheter for the purpose of keeping this open during the first few days after operation.

These various impressions have recently been crystallized in my mind by the following experience:

B. F., an Irish laborer, 38 years of age, entered St. Vincent's Hospital in February, 1916, with the following history:

One week previously he was in perfectly good health, and had never suffered any venereal disease, or any disease referable to the urinary organs. On that day he had occasion in the course of his work to sit for two hours on a board covered with ice. Immediately thereafter he felt quite a severe pain in the left loin, which lasted a few hours and then disappeared entirely. That night he urinated, but from then on for six days he had not urinated a single drop. He had been repeatedly catheterized and no urine obtained. He was beginning to feel a little sleepy, but otherwise thought himself quite well.

Physical examination revealed a vigorous physique, a moderate over-distention of the intestines (although he said his bowels had moved daily), a systolic blood pressure of 170, a coated tongue, no palpable disorder in the urinary tract, the kidneys insensitive and impalpable.

The X-ray showed a very large left kidney, and no kidney shadow on the right side.

A few hours after his admission to the hospital he was catheterized, and no urine obtained. By this time he had become slightly cyanotic, and was a little irrational.

Cystoscopy revealed an absolutely empty bladder, the trigone a little blue (apparently corresponding with the general congestion of his body). A 6 F. ureter catheter was inserted readily 30 cm. up the left ureter, and obtained not a single drop of urine. Since it seemed probable that the end of the catheter must be in the kidney pelvis, its function was tested by the injection of a 2 cc. boric acid solution, which was promptly returned but without any addition of urine. A No. 6 F. ureter catheter was inserted 5 cm. up the right ureter. Since this would go no farther, smaller catheters were tried, and finally a filiform bougie, but none of them passed more than 5 cm.

The patient was accordingly promptly turned upon his left side, and the right loin opened by the usual oblique incision. The loin was very thoroughly searched from liver to beyond the pelvic brim, and no trace of kidney or ureter found. The incision was accordingly closed around a small tube, and the opposite loin opened, revealing a very large and deeply congested kidney. Through a small puncture in the convex border of this a tube was inserted into the pelvis, whereupon 20 to 30 cc. of urine gushed forth under considerable pressure. The pelvis was palpated and the upper ureter (which felt quite normal) was also felt but not very carefully exposed. No stone was discovered, and the wound was therefore closed around the kidney drainage.

The immediate convalescence was a trifle stormy; the patient had a dry tongue, and was distinctly flighty and stupid by turns for about two days, after which he recovered without any further complications.

For a week he passed no urine from the bladder, but at the end of this time, to my great surprise, he passed on a single occasion about 300 cc. of urine. He then began to run a rather irregular temperature, and would pass urine at irregular intervals, usually about once a day. Cystoscopy was accordingly again performed, and the bladder found to contain almost pure pus from which the streptococcus was cultivated. Meanwhile the urine from the kidney sinus was almost clear.

Under bladder irrigations with silver nitrate this infection of the bladder promptly cleared up.

March 20, 1916. He was now urinating about 400 cc. every night from the bladder, but nothing by day. I accordingly clamped the loin tube, and he began to urinate about a liter in the twenty-four hours.

March 23. Loin tube out.

March 25. Very little urine now was coming from loin; patient was urinating three times a night, and every hour by day with some pain.

March 27. The loin sinus seemed to be closed.

March 30. Temperature rose to 105° yesterday; then the loin opened, the tube was replaced, and the temperature subsided.

Subsequent to this I made an attempt to insert a ureter catheter into the kidney pelvis, but could not do so. Injection of thorium through the loin sinus filled the pelvis of the kidney, but did not pass into the ureter. The tube was therefore left in the nephrotomy wound, and the patient sent home to recuperate.

July 18, 1916. No further urine having been passed from the bladder, and the patient remaining entirely well with the tube in his loin, he re-entered St. Vincent's Hospital for operation.

Before operation an intravenous injection of phenolsulphonephthalein showed in the urine in four and one-half minutes, 25 per cent was excreted in thirty minutes thereafter, and 11 per cent more in the following sixty minutes.

Under ether anesthesia the left kidney was exposed through an oblique incision running parallel and close to the old wound. The kidney was still extremely large (doubtless congenitally so), adherent all about, and with the nephrotomy hole through the center of its cortex. In order to free the kidney it was necessary to deliver it by stripping off its fibrous capsule. This was then cut through about the pedicle, revealing the kidney pelvis and ureter. The ureter, below the kidney pelvis, was found chronically inflamed and slightly dilated, although a probe could be readily passed through it down into the bladder. But on attempting to pass the probe upward into the kidney pelvis it was stopped by a stricture at the very junction of ureter and pelvis, in the midst of a mass of adhesions. A probe was accordingly passed into the kidney pelvis through the nephrotomy wound, and projected against the ureteral orifice. Upon the point of this probe the kidney pelvis was incised, and this incision carried vertically through the stricture of the ureter. Inasmuch as no lumen could be demonstrated in the ureter the effort to cut through only one wall, and to spare the opposite wall of the ureter, was only approximately successful.

There were now two incisions in the ureter and kidney pelvis. The first (which we shall denominate No. 1) in the upper ureter; the second (No. 2) beginning about 2 cm. above this, and extending through the strictured portion of the ureter, and into the kidney pelvis. A rubber tube was inserted into incision No. 1, passed up the ureter, out through incision No. 2, and in again to the kidney pelvis, so that it acted both as a drain to the kidney pelvis and as a splint to keep No. 2 open, while it issued from the ureter in incision No. 1. The nephrotomy wound was then closed by two deep catgut sutures in the parenchyma, a large tube led down to the ureteral and pelvic wounds, and the parietes closed in layers.

Convalescence was uneventful, the small splinting tube was removed on the third day, the large tube on the sixth day.

On the fourth day the patient began to urinate.

On the seventh day the temperature suddenly shot to 104°, and remained there for three days thereafter with a good deal of pain in the left iliac region (at this time most of the urine was coming from the urethra). Then a small phosphatic stone was passed, the temperature promptly came down, and all the urine came through the urethra thereafter.

The patient was out of bed on the twelfth day, and left the hospital healed on the twentieth day.

December 18, 1916. The patient has been in perfect health since his operation.

The following conclusions may be drawn with some degree of certainty from a study of this case:

The patient had a congenital absence or total atrophy of the right kidney, and the left kidney was congenitally hypertrophied.[1] The cause of the anuria is not quite clear; it was probably due to ureteral kinking from mobility of the large kidney. There was no trace of stricture at the upper end of the ureter, nor indeed of any adhesions there, at the time of the first operation. Doubtless the stricture and the adhesions resulted in part from the trauma of operation, in part from the streptococcus infection that followed. The small phosphatic ureteral stone is also believed to have been secondary to this infection. This much at least is certain, that the ureter was not completely blocked after the first operation, for a certain amount of urine could escape down the ureter more than a month thereafter.

Hence it seems not improbable that the nephrotomy was the actual cause of the ureteral stricture which was relieved by the subsequent pyelo-ureterotomy. No attempt was made at any plastic operation because the tissues were so gravely inflamed and so much adherent that any plastic procedure seemed likely to fail. It is, of course, still quite possible that the stricture might recontract, but it has not done so up to the present.

It is, therefore, at least possible that a nephrotomy may be the cause of a ureteral stricture. It is also probable that, in some instances at least, the slow healing of nephrotomy wounds is due to blocking of the upper ureter by pus or blood that accumulates in the kidney pelvis. Why, therefore, since ureteral and pelvic wounds heal so kindly, should we not always drain through the kidney pelvis rather than through the parenchyma?

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[1] *Absolutely total* anuria, if due to ureteral stoppage, is a sign of the absence of one kidney.

During the past six months I have thrice opened the kidney parenchyma for the extraction of stone, and then deliberately inserted a probe into the kidney pelvis, and upon this opened the pelvis widely, inserted a rubber tube there for drainage, and closed the parenchyma by suture. Each one of these cases has healed with the promptness characteristic of a pyelotomy; one of them with surprising promptness, for the wound became gravely infected with staphylococci from the kidney, and nevertheless all trace of urine coming from it disappeared within eight days, though the wound has been about four weeks in healing.

It seems, therefore, possible, not only that pyelotomy is to be preferred to nephrotomy for extraction of stone, etc., when this is possible, but that when nephrotomy is done it may seem wiser to suture the incision in the kidney parenchyma and to drain through a counter-incision made in the kidney pelvis.

A CONTRIBUTION TO THE PHYSIOLOGY OF THE URETER AND THE VAS DEFERENS

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In the course of the last two years the author has been engaged in an extensive and intensive investigation of the action of a large number of drugs on the ureter and the vas deferens, the results of which have in part already been published (1, 2, 3, 4) and in part are to appear later. Although the researches were primarily of a pharmacological character, the behavior of those organs towards various reagents, physical and chemical, and under various conditions incidentally brought to light much interesting information concerning the physiology of the ureter and vas deferens. In the present paper it is proposed to summarize briefly the chief physiological data thus obtained, and to report some new findings.

METHODS OF STUDY

The movements and behavior of the ureter were studied in three ways. First and most important of all, experiments were made with segments and rings of excised ureters. The ureters of dogs, cats, rabbits, oxen and especially pigs were employed. It was found that longitudinal segments of the ureter were not as suitable as rings, and that the most convenient preparations for study were rings of the pig's ureter.

Secondly, the behavior of the ureters was studied by direct inspection of the ureters *in situ* in laparotomied animals. The rabbit was found to be the most convenient animal for this purpose, as the ureters in it are large, easily exposed, and are not concealed by excessive amounts of fat.

Lastly, whenever practicable, observations were made *in vitro* on rings of human ureters obtained from cases of nephrectomy.

It was found that the results obtained by all the methods employed agreed with each other.

The behavior of the vas deferens was studied in the same way: first, on excised vasa deferentia of dogs, cats, rabbits, guinea-pigs and rats; second, by observations *in situ*, in rabbits and guinea-pigs under anesthesia; and lastly, on segments of human vas whenever obtainable from the operating room. Unlike the ureter, in which ring-preparations were found to be much better adapted to the study of ureteral contractions than longitudinal strips, in case of the vas ring-preparations were found to be unsuitable for experimentation, and all the observations were made on longitudinal segments of the organ. As in the case of the ureter, so in the case of the vas deferens, the results obtained by the different methods of study agreed with each other.

ON THE MOVEMENTS OF THE URETER AND VAS DEFERENS

a. Normal contractions. When an excised ureter is suspended in a suitable oxygenated medium, to be described presently, at a proper temperature, it will after a period of from thirty minutes to one hour, and sometimes sooner, begin to exhibit spontaneous rhythmic contractions. A most convenient method of studying these contractions is by means of ring-preparations. Such an ureteral ring will "beat" for hours with surprising regularity at the rate of from five to seven times per minute and will inscribe a curve on the kymograph not unlike that made by a beating frog's heart. In this way, the *rate* and *strength* of the ureteral contractions or peristaltic movements, as well as its *tonus* may be studied under normal conditions on the one hand, and under the influence of various agents, physical or chemical, on the other (figs. 1 and 2).

b. Vitality of the ureter. It is interesting to note the remarkable vitality of the excised ureter. Just as the author found that he could preserve alive the pulmonary and other arteries for a long time after excision (5), so also in the case of the ureter it was possible to revive the contractions of that organ as late as forty-eight hours after excision, provided the tissue was preserved in a suitable solution and kept in a refrigerator.

In case of the vas deferens, suspension preparations under suitable conditions, were also found to exhibit rhythmic contractions, but these movements are not so constantly and not so easily obtained as in case of the ureter. Only longitudinal segments of the organ and not rings, were found to exhibit these movements.

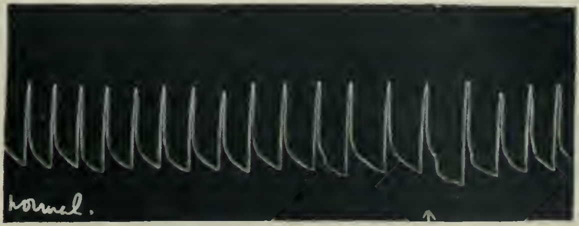

Fig. 1. Ring of Pig's Ureter Six Hours After Death

Experiment, January 12, 1916. Showing normal contractions in normal Locke's solution. Contraction = up-stroke; four beats per minute.

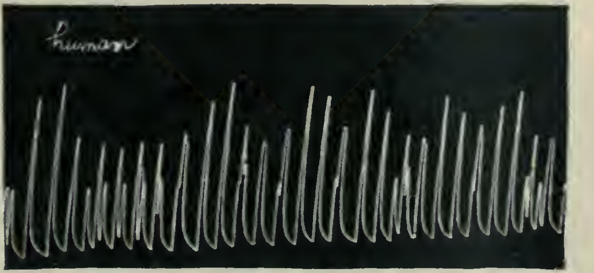

Fig. 2. Human Ureter

One ring; four hours after nephrectomy for hydronephrosis on December 15, 1915; showing spontaneous contractions. Contraction = up-stroke, seven beats per minute.

c. Suitable media. For the study of the spontaneous contractions of the isolated ureter, the preparations must be suspended in Locke's solution, which is a modified Ringer's solution plus dextrose. In ordinary Ringer's solution the contractions are not as active, while in normal NaCl solution the tissue quickly dies and the contractions cease. A still better medium is obtained by the addition of small quantities of urea (0.2 to 0.4 per cent) to the Locke solution (fig. 3). The optimum medium for the study of the isolated ureter, however, is a mixture of Locke solution with fresh (acid) urine in proportion of about 10 to 1. The addition of a little urine to a Locke solution in which a quiescent ureter is suspended may be sufficient to start up its contractions. After considerable experimentation it was learned that the superiority of a urine-Locke mixture over a simple urea-Locke mixture, is due to the greater hydrogen ion concentration of the former. It appears that a slightly acid medium is necessary for the maintenance of normal ureteral contractions. Thus, in Tyrode's solution (6) which is of a lesser hydrogen ion concentration than Locke solution the ureter beats very poorly, while the addition of a minute quantity of alkali (sodium bicarbonate) stops the contractions altogether (fig. 4).

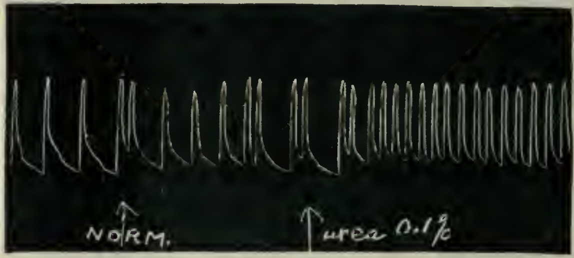

Fig. 3. Ring of Pig's Ureter Twenty-Four Hours After Excision

Experiment January 13, 1916. Showing normal contractions in Locke, and the improvement of the same by addition of urea 0.1 per cent. Contraction = upstroke; normal four beats per minute; after urea seven beats per minute.

Exactly the reverse holds good for the vas deferens. Here it was found that the vas exhibits its movements better in Tyrode's solution, than in Ringer's or Locke's, and that the addition of a little alkali (sodium bicarbonate) improved the contractions still more. Thus it is seen that for the contractions of the ureter a slightly acid medium is the optimum, while for the movements of the vas deferens, on the contrary, a slightly alkaline solution is most suitable. If we bear in mind that in most higher animals the urine is acid, while the spermatic fluid is alkaline, we cannot fail to note the striking agreement of the movements in vitro just studied with the conditions prevailing in the living body (fig. 5).

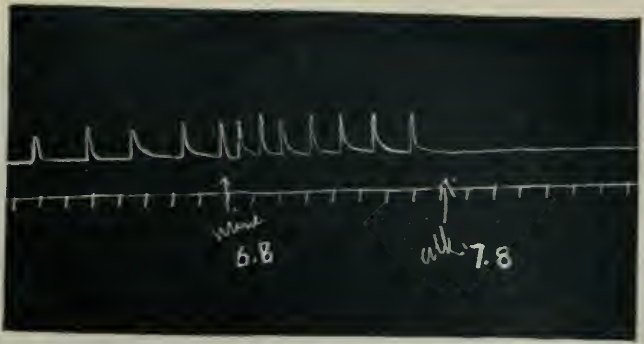

Fig. 4. Pig's Ureter

Twenty-four hours old in Locke's solution. Showing improvement in contraction through addition of fresh urine to the Locke, making the P_H 6.8, and the inhibition of contractions produced by adding sodium bicarbonate making the P_H 7.8. The P_H was determined colorimetrically by Marriott's method.

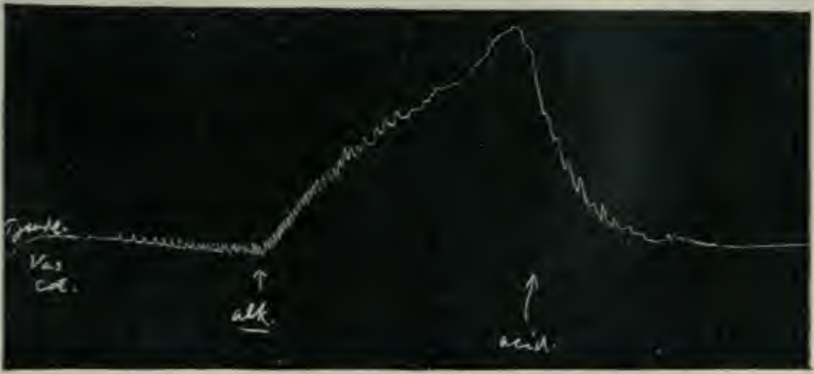

Fig. 5. Vas Deferens of Cat, in Tyrode's Solution

Addition of sodium bicarbonate improves the contractions. Introduction of acid sodium phosphate inhibits them.

d. Oxygenation. A proper oxygenation or aëration of the ureteral vas preparations is essential for the maintenance of their activity. Lack of oxygen was found to diminish their contractions both in strength and frequency. This was improved by restoring the oxygen supply.

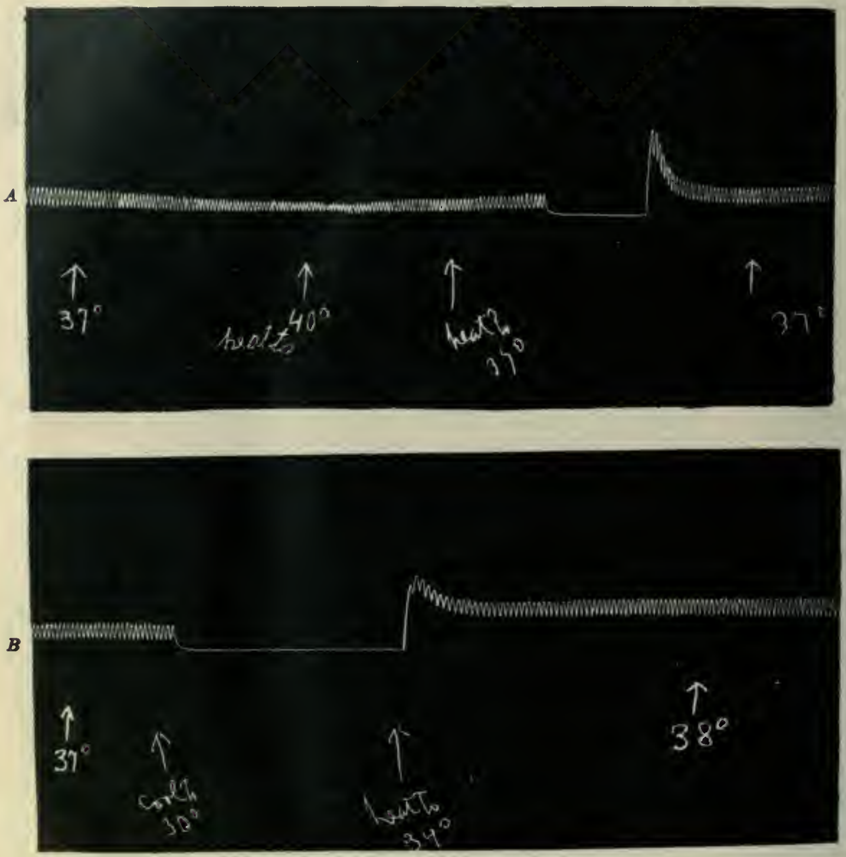

Fig. 6. Ring of Pig's Ureter Three Hours After Death

Experiment December 21, 1915. *A*, showing effect of heating; *B*, showing effect of cooling. Speed of drum, about six beats per minute at 37°C.

e. Effect of temperature. The effect of temperature on the ureter and vas deferens is interesting and important. The optimum temperature was found to be about 37°C. Variations in temperature between 34° and 38°C. produced but little change in the rate or force of the contractions. Higher and lower temperatures, however, markedly affected the movements. When the temperature is gradually raised there is first a stimulation of the contractions, but on further increase the movements are paralyzed, 41°C. being the upper limit. Still higher temperaures will kill the protoplasm. On gradually lowering the temperature below 37°C.. the movements are slowly inhibited and at 30°C. they are paralyzed entirely. Restoring the temperature to normal, however, tended to revive the contractions (fig. 6).

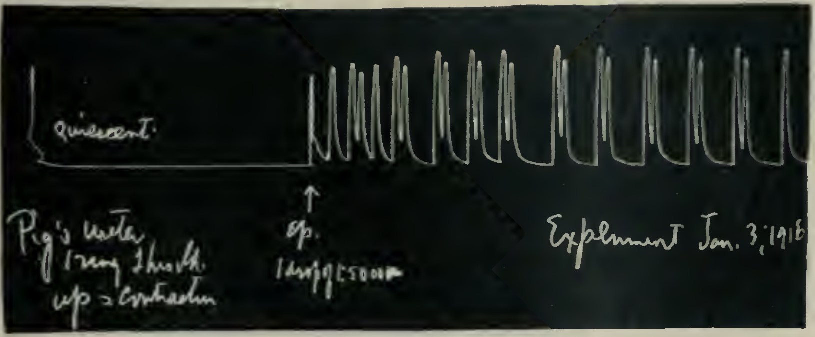

FIG. 7. QUIESCENT URETERAL RING

From pig stimulated to powerful contractions by a minute dose of epinephrin. 1 drop of 1:5000 solution in 25 cc. of Locke.

PHARMACOLOGICAL DATA ON THE INNERVATION OF THE URETER AND VAS DEFERENS

a. General. The action of drugs on the ureter and vas deferens is interesting not only from the pharmacological point of view, but also from the physiological, as throwing light upon the still somewhat unsettled question of the innervation of those organs. Thus for instance Langley and Anderson doubt the existence of a parasympathetic nerve supply to the vas deferens (7). As is well known, certain drugs attack only certain specific nerve endings, and by the employment of such drugs evidence as to the kind of innervation of those organs can be obtained which is as valuable as that derived from careful dissection and histological examination.

b. Action of epinephrin. When a minute quantity of epinephrin (one drop of a 1: 10,000 solution) is introduced into a chamber filled with 50 cc. of Locke's solution and containing an ureteral ring preparation, a striking effect is soon noticed. The ureter begins to contract more frequently and more vigorously, and its tonus is distinctly increased. Such a small dose of epinephrin will start powerful contractions in an otherwise quiescent ureter (fig. 7). Larger doses of epinephrin exert a correspondingly greater influence on the ureteral ring. The contractions become very rapid, and at the same time very short, owing to the greatly increased tonicity. Indeed the ureter finally passes into a condition of tonic contracture or tetanus (fig. 8). This lasts for an hour or more and gradually wears off, as the drug is oxidized, until the contractions become normal again.

The vas deferens and seminal vesicles are stimulated by epinephrin both in respect to contraction and tonicity in exactly the same way (fig. 9).

It is well known through the study of Langley and Elliott (8) that epinephrin is our principal drug attacking all true sympathetic or dorsal-lumbar autonomic (Langley) nerve endings, or as some prefer to express it myoneural junctions—whether pressor or depressor, accelerator or inhibitor, constrictor or dilator, wherever they may be, and stimulating them to greater activity just as an electric current would do. The response of the ureter and vas deferens to epinephrin is therefore proof positive of their innervation by the true sympathetic. This is further corroborated by their behavior towards ergotoxin.

c. Action of ergotoxin. This important constituent of ergot is also a sympathetico-mimetic drug affecting the true sympathetic. As a result of the work of Barger and Dale (9) its physiological effects are of a twofold nature, as follows:

(a) A stimulant effect on plain-muscular organs, prominent among which are contractions of the arteries, the uterus, and the sphincter of the iris.

(b) A specific paralysis of the *motor* elements in the structures associated with sympathetic innervation, which adrenalin stimulates; the inhibitor elements retaining their normal function, as do also both motor and inhibitor autonomic nerve supplies of cranial and sacral root origin.

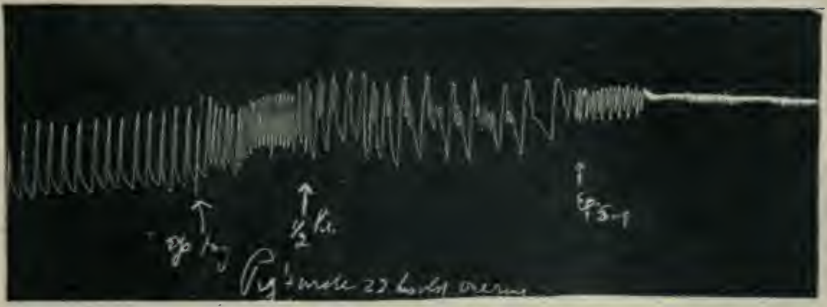

FIG. 8. PIG'S URETERAL RING TWENTY-TWO HOURS AFTER EXCISION

Showing stimulating effect of 1 mgm. epinephrin in 30 cc. Locke; wearing off of effect one-half hour later; and powerful tonic spasm from 5 mgm. of epinephrin.

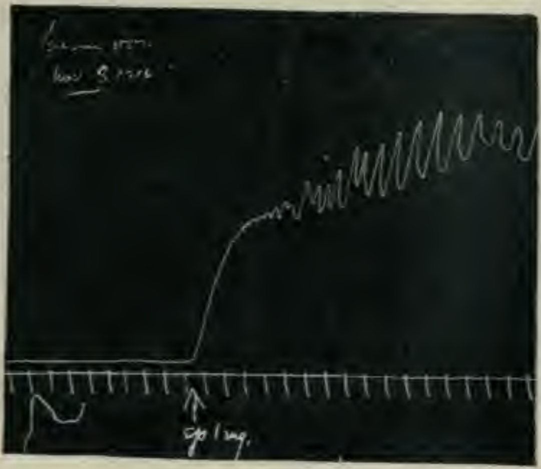

FIG. 9. HUMAN VAS DEFERENS

(From the operating room.) Segment 1 cm. long. Showing stimulating effect of epinephrin, 1 mg. in 50 cc. Locke.

As a result of this peculiar selective action, the effect of epinephrin on those organs which are supplied with both motor and inhibitor sympathetic terminals, as for instance the arteries of carnivora, and in which ordinarily epinephrin produces a motor effect, is *reversed* by ergotoxin. Thus an animal which is first injected with ergotoxin, will respond to a subsequent injection of epinephrin with a fall instead of the ordinary rise in blood-pressure, because the motor-terminals having been paralyzed by the ergotoxin, the suprarenal principle can act only on the inhibitor terminals which are still intact.

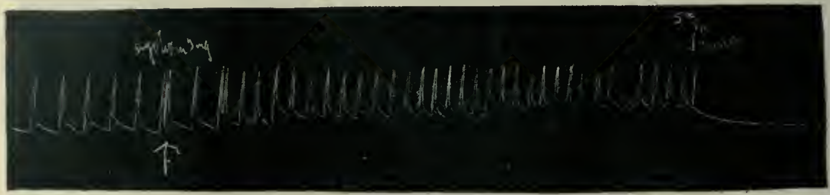

FIG. 10. PIG'S URETER

Experiment January 12, 1916. One ring in urine-Locke (1: 10). Showing effect of ergotoxin 5 mgm. and reversal of epinephrin action following same. Contraction = up stroke.

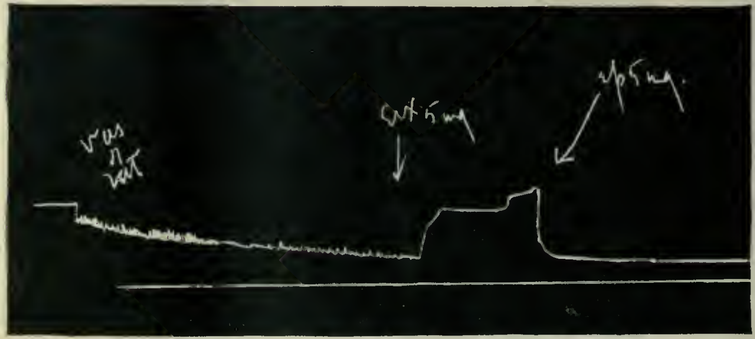

FIG. 11. VAS DEFERENS OF RAT

Showing reversal of epinephrin effect by previous administration of ergotoxin.

When an ureteral or vas deferens preparation is treated with 1 to 2 mgm. of ergotoxin phosphate in 50 cc. of Locke, there is noticed a primary stage of stimulation as indicated by an increase in tonus and in the rate of contractions. This is followed by a slowing of the contractions and relaxation of tonus, especially larger doses of ergotoxin are used. If now the ergotoxin is followed by a dose of epinephrin, it is interesting to find that the motor effect of epinephrin is inhibited, and indeed a slight relaxation is noted. In other words, the ureter and vas exhibit a reversal of epinephrin action after ergotoxin in exactly the same way as an artery would do. This furnishes an additional proof of a true sympathetic innervation of these organs (figs. 10 and 11).

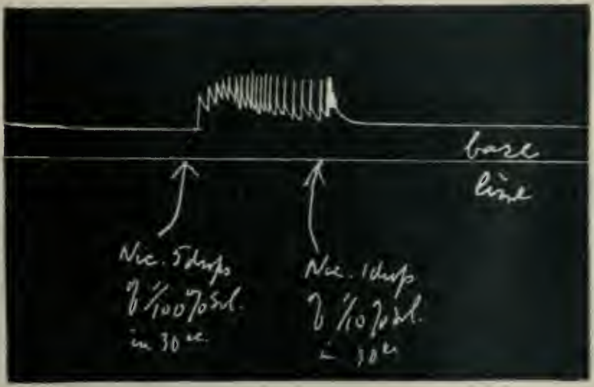

Fig. 12. Ring of Pig's Ureter

Experiment January 26, 1916. Forty-eight hours after death of animal. Showing how the quiescent ureter is first stimulated by 0.01 per cent of nicotin and secondly, paralyzed by 0.1 per cent nicotin solution.

d. Action of nicotin. Nicotin is endowed with the well-known selective action on ganglion cells, which it first stimulates and later paralyzes. Its effect on the ureter was found to be the same as on other organs; e.g., the heart. Small doses of nicotin or its salts stimulated the contractions and increased the tonus of the ureter; larger doses paralyzed it (fig. 12). This response to nicotin points to the existence of ganglionic structures in that organ, and agrees prettily with the anatomical findings of Dogiel (10), R. Maier (11), and Protopopoff (12). The author did not study the effect of nicotin on the vas, but in a recent paper by

Waddell (13) that observer reports a similar behavior of that organ.

e. Action of drugs affecting the sacral autonomics. Just as epinephrin and ergotoxin are drugs affecting specifically the myoneural junctions or nerve-endings of the dorsal-lumbar autonomics or so-called "true sympathetics," so too there is another group of drugs which acts specifically upon the nerve-endings of the cranial-bulbar-sacral autonomics or the so-called "parasympathetic" nervous system. The principal pressor or accelerator drugs of this group are pilocarpin, physostigmin, muscarin, and cholin; the chief depressor or inhibitor drug of the group is atropin.

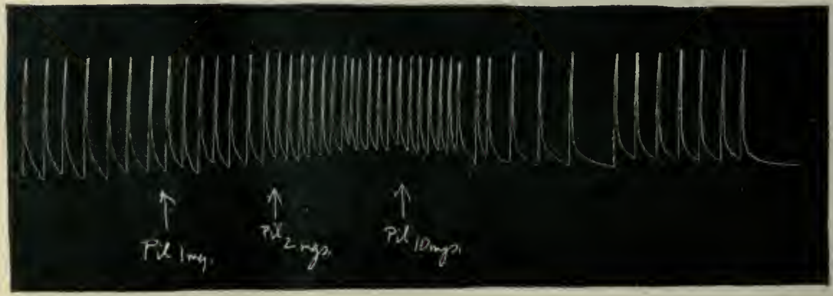

FIG. 13. ACTION OF PILOCARPIN

Pig's ureter six hours after death of animal

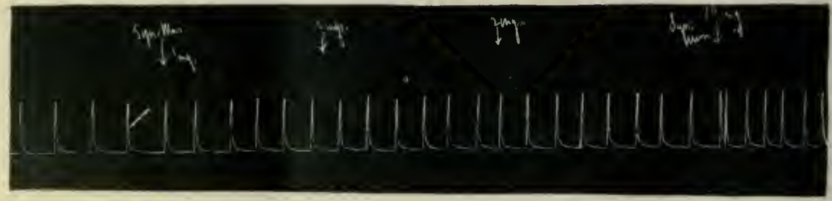

FIG 14. RING OF PIG'S URETER

Twenty-four hours after death of animal. Action of pseudomuscarin or synthetic muscarin.

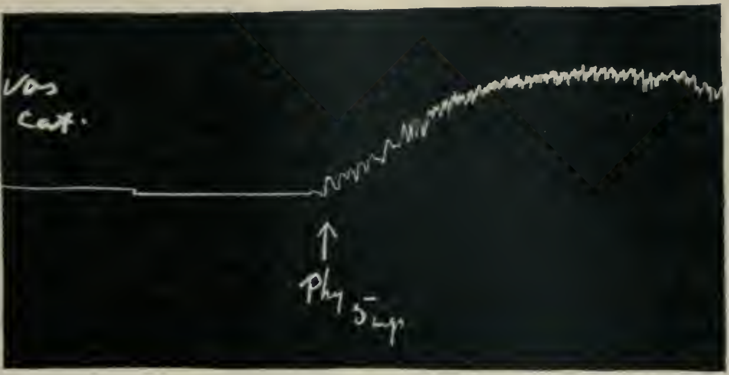

FIG. 15. VAS DEFERENS OF CAT

Showing the stimulating effect of physostigmin hydrochloride (5 mgm. in 50 cc.) in a quiescent preparation.

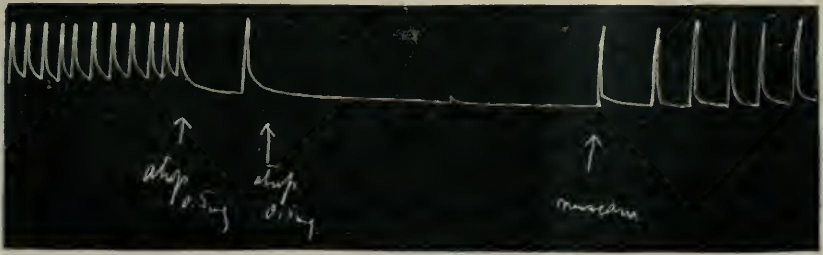

FIG. 16. RING OF PIG'S URETER

Twenty-four hours after excision. Showing inhibition by atropin and antagonizing action of muscarin (1 cc. of aqueous extract of fungus).

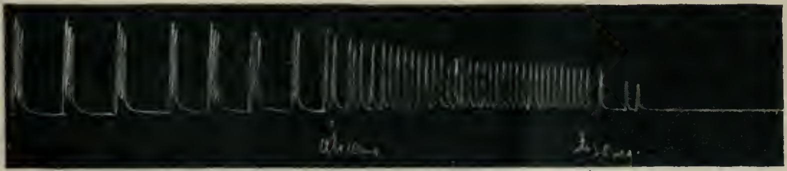

FIG. 17. RING OF PIG'S URETER

Twenty-four hours after excision. Primary stimulation of frequency of contractions and subsequent inhibition after atropin.

The behavior of the ureter and vas deferens under the influence of these drugs gives evidence of those organs being innervated by the sacral autonomic or parasympathetic fibers, as well as by the true sympathetic already noted. It was found that pilocarpin, physostigmin, muscarin and cholin, all produced stimulation of ureteral and vas deferens preparations. These findings were further confirmed by observations of the organs in situ in anesthetized animals (figs. 13, 14 and 15).

f. Action of atropin. The effects of atropin, when given in sufficiently large quantities, is to antagonize the action of the above drugs and to inhibit the contractions. It was curious to note, however, that small doses of atropin tended at first to stimulate the contractions of the ureter and the vas. The probable explanation of this phenomenon was advanced by the author at the annual meeting of the Federation of American Societies for Experimental Biology, in New York, December 28, 1916. The author showed that atropin being a *racemic* form of hyoscyamin is a mixture of l-hyoscyamin and d-hyoscyamin, and that while l-hyoscyamin stimulates the ureter, the dextro-gyrate form tends to inhibit it. The full discussion of this peculiar action will appear later in the Journal of Pharmacology and Experimental Therapeutics (figs. 16 and 17).

SUMMARY

The results of the above investigations may be summarized as follows:

1. The behavior of the ureter and vas deferens was studied, firstly on surviving excised organs, secondly by observations of those organs in situ, in the living body, and thirdly on excised human ureters and vasa deferentia after operation.

2. The isolated ureter contracts best in a slightly *acid* medium; the isolated vas contracts best in a slightly *alkaline* medium. This corresponds to the natural conditions in the body.

3. A rise in temperature at first stimulates and subsequently paralyzes the contractions of the ureter and vas. A fall in temperature inhibits the contractions.

4. Adequate oxygenation is essential for the maintenance of the contractions of the ureter and vas deferens in vitro.

5. The response of the ureter and vas to epinephrin and ergotoxin is an evidence of their innervation by the dorsal-lumbar or true sympathetic nervous system.

6. The response of the ureter and vas to pilocarpin, physostigmin, muscarin, cholin and atropin is an evidence of their being also innervated by the sacral autonomic or para-sympathetic nervous system.

7. The response of the ureter and vas to nicotin points to the presence of ganglion cells in the walls of those organs.

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THE EFFECT OF CALCIUM, WATER AND OTHER SUBSTANCES GIVEN INTRAVENOUSLY ON BLOOD COMPOSITION AND URINE SECRETION

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In treating of the secretion of urine, it has been customary to select for study the point of exchange between the tissues and the blood, where katabolites are turned over to the common carrier, and the point of exchange between the blood and the urine, where the waste products are finally put in the form in which they are to be expelled. Concerning the organ which is the seat of the latter exchange, the kidney, we must gain our information for the most part by indirect methods. Perhaps the most obvious one, and the one which has been followed by very many investigators, is the inquiry into the conditions surrounding its work through analysis at various times of the blood and urine. In spite of the quantity of such work which has been done, the laws governing the quantitative and qualitative secretion of urine remain obscure and it is felt that further efforts along these lines using new and accurate experimental and analytical methods may not be superfluous.

The literature of this subject is familiar enough so that reference need be made only to those investigations which have led up directly to the present work.

Magnus (1) attempted to determine what conditions in the blood are responsible for diuresis. He noted that hypotonic, as well as hypertonic or isotonic salt solution given intravenously will cause diuresis, and it seemed to him at first that hydremia was the sine qua non of diuresis. Later it was observed that diuresis could outlast hydremia, and he concluded that an increase in the content of any excretable substance in the blood determined diuresis. Other cases described by Magnus in which a certain amount of hydremia persisted after the cessation of diuresis would seem to the writer to make this conclusion untenable, since they present an increase in the urinary constituent water in the blood without diuresis. These findings have been reiterated by many others (Thompson (2), Sollmann (3), Tropp (4)).

However it is the rule that copious diuresis is usually associated with a certain degree, less than might be expected, of hydremia. It seems to the writer, therefore, that experiments showing to what extent changes in the composition of the blood can be brought about without diuresis may throw more light on the subject than those in which it occurs freely. One method of doing this is suggested by the work of Magnus (5), who injected whole blood, and of Ponfick (6), v. Limbeck (7), Knowlton (8), Fischer (9), Roger and Garnier (10), etc., who injected solutions of gelatine and other colloids without diuresis.

It seems that colloid materials, such as gelatine and plasma proteids, hold water in the circulation through some affinity, since it does not leave the vessels readily, either through the kidneys or into the tissues when injected in combination with these substances. The exact nature of this affinity remains to be described, but it is probable that it may be varied by changes in the concentration of other substances in the blood stream in a manner analogous to that in which the water affinity of gelatine jellies is varied by electrolytes. However, this problem too is difficult to solve since any substance introduced into the circulation has opportunity to act on the kidney epithelial cells also, which may equally well alter urinary secretion. While this circumstance apparently eliminates the possibility of an experimentum crucis, it does not prevent our studying the composition of the blood under as many and different conditions as possible, and trying to evolve general laws from such studies. If we utilize in our experiments only excretable substances, we may probably be able to consider the plasma proteids as a constant factor, varying in their influence on renal secretion only as their affinity for water is varied by the crystalloids present.

The injection of colloid substances, however, was not considered suitable for the purposes of this work. Among other possible procedures, the experiments of Woodyatt (11) offer a promising means of introducing water without diuresis. They make evident a clean-cut relationship, taking into account body weight and time, between unit intake of glucose, given intravenously, and unit output, provided the intake is not less than 0.85 gram of glucose per kilogram hour, in which case there is neither diuresis or glycosuria.

A third method available is the intravenous injection of distilled water, which, as noted over sixty years ago by Kjerulf (12) and subsequently by Hermann (13), Westphal (14), v. Limbeck (7), Frey (15), Sherrington and Copemann (16), Fischer (9) and others, causes no increase in urinary flow. In other words, water, under these conditions, when it reaches the circulation in the pure state is not a diuretic. When such an experiment is performed, the injection may be easily pushed until the death of the animal occurs from the overloading with water. This absence of diuresis under experimental conditions does not of course mean that the excretion of water is a matter of total indifference to the body, but on the contrary that the mechanism for the purpose requires the interaction of other substances in order to precipitate, under natural conditions, the necessary diuresis. In such cases the excess fluid is all actually removed within the next twelve hours after the injection, if the animal survives. Here then is an excellent opportunity to study such interaction among the urinary constituents.

In the consideration of saline diuresis, it is a common thing to assume that osmotic pressure is an important element in the production of urine. The theory has been put forward that the diuretic action of a salt is a function only of its osmotic pressure. A priori, this has seemed improbable to the writer, and, in an effort to devise an experiment bearing on this point, calcium was selected as the most antagonistic in its action to the commonest example of the diuretic salt, sodium chloride. This antagonism has been demonstrated in many different ways, both biological and physical chemical. MacCallum (17) has offered evidence in favor of an inhibitory action on renal secretion. Clowes (18) assumes that in the case of a bivalent substance like calcium, the anion action predominates, while with the monovalent sodium, the cation action is in the foreground, and that cation and anion are always antagonistic. Whether this hypothesis is correct or not the injection of fluids in which $CaCl_2$ was substituted for part or all of the NaCl of physiological salt solution gave rise to a secretion of urine which exceeded the normal by little or nothing.

This then gives a choice of three methods of introducing considerable quantities of fluid containing no colloidal substances into the veins without evoking diuresis.

In carrying out the elementary experiments described below the suggested lines were followed; first, to introduce distilled water intravenously at a constant rate, which procedure produced no diuresis, and second, to introduce solutions of glucose, $CaCl_2$, or mixtures of the latter with NaCl so arranged as to produce no diuresis. The object of the first type of injection was to discover what changes in the water content of the blood might occur without diuresis, and the second, to discover what additional changes in the concentration of the other substances in the blood might occur without diuresis. There is also included one injection of 0.4 per cent NaCl solution which was accompanied by diuresis.

The solutions were all introduced intravenously in dogs over fairly long periods of time at uniform rates by an electric pump modelled after that of Woodyatt (11), since it was thought that this method offered great advantages for a study of this sort. The conditions of its use will be discussed later.

The experiments are classified under several heads, according to the composition of the fluid which was injected.

The technique was as follows: Injections were always made without general anesthesia of any sort. Whenever practicable, a needle was inserted through the skin into the saphenous vein and held in place by adhesive plaster. When this could not be done, a small incision was made under local anesthesia with distilled water, and cannula or needle introduced directly in the vein. The fluid was carefully warmed before injection. Blood was drawn with pipet and needle from the jugular vein. With animals accustomed to the procedure, as they all were, this causes no apparent disturbance, and there has been no reason to believe that the psychic effects had any serious influence on the results of the experiments. Urine was collected through an ordinary metal catheter, aided by gentle massage of the bladder. The catheter remained in situ during each experiment, and was emptied during and after the massage by a fine flexible tube carried in to its tip, and connected with a suction bottle. There is reason to believe that this procedure empties the bladder completely and certainly.

Water determinations were made gravimetrically, the whole blood being dried at 120°C. to constant weight. This procedure has subsequently been amplified by also drying the plasma after centrifuging in a graduated tube. A small quantity of powdered potassium oxalate necessitating only a very slight correction is used as an anticoagulant. From such data the relative volume and water content of both corpuscles and plasma can be calculated.

For blood sugar determinations, the method of Benedict and Lewis was followed, the heating being done in an autoclave. McLean and Van Slyke's method served for blood and urine chlorides. Hemoglobin percentages were usually determined in an ordinary Sahli hemoglobinometer, but in the single chloride experiment, 0.5 cc. of fresh blood was placed at the beginning of the experiment in a 100 cc. volumetric flask with 0.5 cc. 5 per cent HCl, the flask filled to the mark and set aside in the cold box. At the end of the injection it was compared in a du Bosc colorimeter with another preparation made in the same way. This gives the relative hemoglobin percentage, the initial or normal value being expressed as 100, with great accuracy. The absolute value would be of no advantage in these experiments.

Freezing point determinations were made with defibrinated blood in an ordinary Beckmann apparatus, in some cases fitted with a tube which allowed smaller quantities of blood to be used.

Blood urea was estimated by Marshall's urease method.

I. INTRAVENOUS INJECTION OF DISTILLED WATER WITHOUT DIURESIS

That injection of distilled water produces no diuresis was confirmed.

Experiment I. Distilled water at different rates, 2 to 250 cc. per hour Injection performed for two hours, gradually increasing rate until 250 cc. per hour was reached. Urine remained constant at about 2 cc. per hour. Hemolysis occurred. Dog apparently not injured.

Experiment II. Distilled water at rate of 50 cc. per kilogram hour, followed by 2 per cent salt solution.

	MINUTES	URINE
		cc.
	30	
	15	1.9
	Before	
	0	1.7
Injection of water: begins	After	
	15	0.6
	30	1.8
ends	38	2.0
Injection of 2 per cent NaCl: begins	45	7.3
	52½	35.0
ends	60	43.0

	HEMOGLOBIN	Δ	BLOOD H_2O
			per cent
Before	100	0.616	79.11
After	80	0.559	81.12

Blood was drawn before the injection commenced and again at the end of thirty-five minutes. After this 2 per cent NaCl solution was run in to determine if the hemolysis had any effect on salt diuresis. Fischer (9) has suggested the "upset of oxidative conditions" resulting from hemolysis as a possible cause of the lack of diuresis after distilled water. In this case, the salt diuresis occurred normally. Frey (15) performed an exactly similar experiment with the same result. Since, however, there is no absolute certainty as to the reason why water causes no diuresis, extensive conclusions can not be drawn from this observation.

As a result of the distilled water, the water content of the blood was increased 2 per cent, while Δ fell 0.057°, the great drop in hemoglobin undoubtedly being largely due to hemolysis.

II. INTRAVENOUS INJECTION OF $CaCl_2$, WITH AND WITHOUT NaCl IN VARIOUS PROPORTIONS, WITHOUT DIURESIS

The most superficial interpretation of the above results would be that there is a simple reciprocal relation in the production of urinary secretion between the water content of the blood and the molecular concentration of the blood in which an increase in one may be neutralized in its diuretic action by a corresponding decrease in the other. Such a compensation would be the one in which the blood is diluted with distilled water.

Working from this tentative interpretation, one would expect that in true saline diuresis, as for example with injection of an isotonic or hypotonic solution, the water content of the blood would be increased, but with no compensatory decrease in the molecular concentration.

The following facts are at our disposal. One intravenous infusion of 0.44 per cent NaCl solution, in which 2260 cc. were injected during one hour in a dog weighing 11.6 kgm. and narcotized with morphine was performed by Magnus (5). Diuresis commenced within ten minutes. At the end of the hour, the serum solids had fallen from 6.34 to 4.61 per cent, and the Δ from 0.590° to 0.509°.

A somewhat similar experiment performed by the writer is tabulated below (Experiment III).

In this experiment the injection is smaller than that of Magnus and the diuresis longer delayed and less in quantity. It is interesting that the fall in the serum dry substance is nearly the same in each (in the one case 6.34 to 4.61, in the other 7.87 to 6.20). The figures for the whole blood show either a great imbibition of H_2O by the red blood corpuscles, or an increase in

Experiment III. Injection of 0.44 per cent NaCl solution at rate of 700 cc. per hour. This is equivalent to 3.08 gram NaCl per hour (0.77 gram NaCl, 87.5 cc. H_2O per fifteen minutes). Weight of dog 11.92 kgm.

	MINUTES	URINE	TOTAL Cl	PLASMA H_2O	PLASMA Cl
		cc.	*grams*	*per cent*	*per cent*
	30	0.7		92.13	0.657 0.645
	15				
	Before				
	0	0.5			
begins	After				
	15	0.45	0.00225		
	30	*0.5*	*0.00225*	*93.26*	*0.675*
	45	2.4	0.01320		
Injection of 0.44 per cent NaCl....................	60	10.0	0.03500	93.59	0.657
	1.15	34.0	0.05440		
	1.30	65.0	0.04530	93.64	0.660
	1.45	85.0	0.09350		
	2.00	148.0	0.18352	93.80	0.660 0.660
ends					

	Hbg.	Δ	BLOOD H_2O	PLASMA H_2O	PLASMA Cl
			per cent	*per cent*	
Before..........................	100	0.572	77.86	92.13	0.651
After..........................	85	0.554	81.12	93.80	0.660

plasma quantity. In the writer's experiment, however, Δ fell only 0.018°.

Greater emphasis is laid on the latter experiment for two reasons. First, the injection continued longer, and second, the experiment was performed without any interference from anesthetic or other drugs. It is desired to lay especial emphasis on this latter point. Bogert, Underhill and Mendel (19) have recently shown that morphine interferes very seriously with the mechanism operating to keep the blood composition constant. It is also well known from the experiences of Thompson (20), Frey (15) and others that such substances as urethane, chloretone, and to a less extent paraldehyde, interfere with renal excretion, and similar objections apply in the case of ether, in addition to its effect in producing hyperglycemia and even glycosuria.

While the experiment shows a slight fall in the Δ, it is characterized by a marked hydremia with no change in the Cl content, and is not absolutely incompatible with the hypothesis outlined. In the course of the writer's work other objections to this hypothesis in its simple form have come to light, but for the moment discussion of them will be deferred.

The next protocol gives the results of an injection in which NaCl was replaced by a quantity of $CaCl_2$ isotonic according to the Landolt-Bjornstein tables with an 0.8 per cent NaCl solution. It was the first calcium experiment, and it was thought possible that it might give a condition of hydremia and increased molecular concentration of the blood, yet without diuresis owing to the effect of the calcium ions on the renal cells. The result, however, was quite different.

Experiment IV. 25 cc. per kilogram hour, 1.2 per cent $CaCl_2$ solution

	MINUTES	URINE
		cc.
	30	
	15	0.75
	Before	
	0	0.5
begins	After	
	15	0.3
Injection of 1.2 per cent NaCl solution.......	30	0.25
	45	
ends	60	0.25

	HEMOGLOBIN	Δ	BLOOD H_2O
	per cent		*per cent*
Before..........................	105	0.575°	77.9
After...........................	116	0.571°	73.85

The dog was uncomfortable from the beginning. Vomited after ten minutes of injection. When released extreme weakness was shown, the dog lying spread out on his belly on the floor. In spite of this, consciousness was retained and there was apparently no pain. Death occurred about two and one-half hours later. At autopsy there was some excess of clear fluid in the peritoneum and pericardium, but not in the pleural cavities. The blood was dark and thick. There were numerous ecchymoses beneath the endocardium and in the thymus. The intestine was suffused and cyanotic, the duodenum hemorrhagic.

It is evident in this experiment, that while the molecular concentration of the blood remained constant, the response of the somatic cells of the body to calcium was entirely different from that to sodium, in that the blood became very concentrated, the total solids and hemoglobin rising markedly. Sufficient salt was left in the circulation to prevent a rise in the Δ, or in other words, it was an isotonic fluid which went to the tissues. This situation, which had been unforeseen, of course prevented the drawing of any conclusions as to the action of calcium on the kidneys, or a comparison of its properties when in the blood with those of sodium chloride. The urine was greatly diminished. In addition, it was evident that the amount of calcium given constituted a fatal dose, and an effort was therefore made to find a combination of $CaCl_2$ and NaCl which would at once prevent hemolysis, cause no diuresis and be non-toxic.

Experiment V. 0.2 per cent NaCl; 0.2 per cent $CaCl_2$; 700 cc. in one hour

	MINUTES	URINE
		cc.
	30	
	15	1.15
	Before	
	0	1.9
begins	After	
Injection of 0.2 per cent NaCl and 0.2 per cent $CaCl_2$	15	2.0
	30	1.4
	45	0.7
ends	60	0.5

	Hbg.	Δ	BLOOD H_2O
	per cent		*per cent*
Before	103	0.581°	77.5
After	104–5	0.553°	78.25

To this end, three different solutions were tried. The first was a mixture of 0.2 per cent $CaCl_2$ and 0.2 per cent NaCl.

A slight hydremia is accompanied by a marked fall in Δ, while since the hemoglobin percentage remains much the same, we may probably assume that no great alteration in blood volume has occurred.

This fluid when injected caused hemolysis, and since the urinary secretion was rather definitely diminished, it was considered advisable to raise the percentage of NaCl sufficiently to avoid hemolysis. Tests in vitro with dogs' corpuscles showed that if to 0.2 per cent CaCl, 0.37 per cent of NaCl were added, no hemolysis resulted.

Experiment VI. 0.2 per cent $CaCl_2$, 0.37 per cent NaCl, 680 cc. in forty-five minutes

	MINUTES	URINE
		cc.
	30	
	15	1.7
	Before	
	0	1.4
begins	After	
Injection of 0.37 per cent NaCl and 0.2 per cent	15	2.25
$CaCl_2$	30	8.7
ends	45	6.0

	Hbg.	Δ	BLOOD H_2O
	per cent		*per cent*
Before	90–95	0.608°	79.05
After	90–95	0.593°	79.35

It is well known that 0.4 per cent NaCl will cause copious diuresis. In this experiment, a large quantity of 0.37 per cent NaCl (0.5 per cent of the body weight, and therefore about 70 per cent of the volume of blood in the body) was injected with only a very slight, almost negligible increase in the urine secreted, this result being accompanied by adding 0.2 per cent of $CaCl_2$. It should be noted that in bringing about this neutralization of the action which NaCl would have had alone, the Ca salt holds the blood composition almost unchanged, a decrease of 0.015° in the Δ, and an increase of 0.3 per cent in the blood water. These changes, further, are in opposite directions and would therefore, according to the hypothesis, tend to neutralize each other in the effect on renal secretion.

A further experiment was made with a stronger percentage of NaCl, to determine if the quantitative relations of the two salts in their action on urinary secretion persisted.

Experiment VII. 0.2 per cent $CaCl_2$, 0.65 NaCl, 700 cc. in seventy minutes

	MINUTES	URINE
		cc.
	30	
	15	0.9
	Before	
	0	0.0
begins	10	1.5
Injection of 0.65 per cent NaCl and 0.2 per cent $CaCl_2$	25	1.7
	40	9.0
	55	18.0
ends	70	18.0

	Δ	BLOOD H_2O
		per cent
Before	0.568°	78.54
After	0.562°	79.80
Forty-five minutes later	0.557°	

This fluid is almost isotonic with the blood. The Δ of the blood remains almost the same throughout, but the increase in NaCl has resulted in a moderate hydremia and a moderate increase in urine secreted. This would indicate that NaCl and $CaCl_2$ oppose each other in a quantitative way, and that the oliguria is not the result of a toxic action of the Ca making diuresis impossible.

If the diuretic power of a substance is purely a function of its osmotic pressure, the first injection of $CaCl_2$ should have caused a diuresis equal to that caused by 0.85 per cent NaCl solution. We are not at liberty however to say that the effect on the kidney was not a function of the osmotic pressure, since it has been disclosed that a very profound effect on the composition of the blood also results from the injection. It is possible, though there is no evidence to support it, that a diuretic effect of Ca on the kidney is masked by this relatively tremendous loss of water from the blood, since all blood changes in experiments of this sort are remarkably slight (Sollmann (3), Tropp (4), Haldane and Priestley (21)).

It should be mentioned here that Porges and Pribram (22) and Mendel and Benedict (23) have denied that calcium exercises an inhibitory effect on urinary secretion. Mendel and Benedict in every case injected the calcium salt in combination with sufficient NaCl to overcome its inhibitory effect, and their experiments do not therefore support their contention. Porges and Pribram, working with rabbits, found a great fall in systemic blood pressure after injections of Ca, and ascribed the anuria or oliguria to this. Such a fall may well occur with massive doses of Ca, as in Experiment IV, but that it does not in the type of experiment to which the others mentioned belong, is shown by an injection in connection with which blood pressure was recorded. In this case ether anesthesia was used given by the intratracheal method. A solution containing 0.25 per cent $CaCl_2$ and 0.34 per cent NaCl was injected at the rate of 30 cc. per kilogram hour for three hours. No increase in urine formation was noted. The blood pressure remained constant, being possibly a few millimeters higher at the end than at the beginning of the experiment. The absence of diuresis, therefore, could not have been due to a fall in the general blood pressure.

Going back to the original hypothesis, no hopeless contradiction appears in these Ca injections. Where diuresis has occurred, there is an increase in the blood water, with practically stationary Δ, and where it has not occurred, Δ has fallen, while the blood water has remained stationary; or, if Δ has risen, there has been great loss of water from the blood.

IIb. INTRAVENOUS INJECTIONS OF SUGAR SOLUTION WITHOUT DIURESIS

A dilute solution of sugar (say 3 per cent) will hemolyze less than distilled water, and was therefore chosen in amounts corresponding to less than 0.85 gram sugar per kilogram hour to provide an increase in the blood constituents sugar and water without diuresis. The records of two such injections are given.

Experiment VIII. 0.65 grams dextrose per kilogram hour in 3 per cent solution

	MINUTES	URINE	URINE SUGAR	URINE SUGAR TOTAL	BLOOD SUGAR
		cc.	*per cent.*	*grams*	*per cent*
	45				
	30	0.6	0	0	
	Before				
	0	1.8	0	0	0.087
begins	After				
	15	1.6	0	0	
Injection of 3 per cent sugar.	30	1.0	0	0	
	45	1.2	0	0	
ends	60	0.8	0	0	0.200
	120	23.0			

Total urine first hour 4.6 cc.

	BLOOD H_2O	Δ OF BLOOD	BLOOD SUGAR
	per cent		
Before	77.07	0.577	0.0870
After	79.42	0.549	0.2000

It will be noticed that in Experiment IX the tolerance of the animal was exceeded during the second and third hours, producing first a glycosuria and later a diuresis, both of slight degree. However, at the end of the first hour in each experiment the same conditions are present. The sugar content of the blood is increased over 100 per cent without diuresis. In the first experiment it is shown in addition that there has been an increase of over 2 per cent in the water content of the blood. In the

Experiment IX. 0.7 gram dextrose per kilogram hour in 3 per cent solution

	MINUTES	URINE	URINE SUGAR	URINE SUGAR	BLOOD SUGAR
		cc.	per cent	grams	per cent
	26	1.2	0		0.0833
	11	0.9	0		
	Before				
	0	0.1	0		
begins	After				
	15	1.4	0		
	30	0.8	0		
	45	0.9	0		
Injection of 3 per cent	60(1 hr.)	1.2	trace		0.2060
sugar................	1.15	0.9	+ Fehling		
	30	4.0	2.53	0.100	
	60(2 hrs.)	12.8	2.92	0.375	
	2.30	28.0	2.70	0.756	
ends	60(3 hrs.)	62.0	1.36	0.840	0.2564

	BLOOD UREA	BLOOD CHLORIDES	BLOOD WATER	HEMOGLOBIN	R. B. C. PER CMM.
	mgm. per 100 cc.		per cent	per cent	
Before..........	34–32	0.662–0.675	77.5–76.8	105	8,000,000
After...........	30	0.575–0.568	78.1–78.2	103	8,000,000

second this increase is only 1 per cent at the end of three hours, when slight diuresis is actually going on. Here unfortunately the Δ is lacking, but in the first the Δ has fallen 0.028°, that is the molecular concentration of the blood is decreased in the experiment where no diuresis occurred.

DISCUSSION

In discussing the preceding experiments, attention is first directed to the importance of the external conditions present in all diuresis experiments. The unfortunate element, always leading to confusion, which enters almost every such experiment, is the anesthetic. This has already been mentioned, but too much emphasis cannot be laid on it. Haldane and Priestley (21) experimented on themselves, for reasons which they describe as "obvious;" possibly they included the consideration that anesthesia was unnecessary. Thompson (20) and Frey (15) have emphasized the important effects of anesthetics and narcotics, while Woodyatt (11) and Fischer (9) have performed diuresis experiments without anesthetics.

From the time the writer's experiments on diuresis were begun, in the winter of 1915–16, it was felt that they must be kept entirely clear of drug influences. It was found comparatively easy to develop a suitable technique. Good tempered, quiet female dogs with conspicuous veins were selected and no difficulty was experienced in making them lie quietly for the duration of the experiment. Blood could be drawn repeatedly from the jugular without any detectable psychic disturbance. The most satisfactory injection method was to make a small incision over the vein with distilled water as a local anaesthetic, insert a small needle in the vein, tie it in place with a singly knotted thread, and fix the butt of the needle with adhesive plaster. At the end of the injection, the thread could be untied and removed and the needle withdrawn, which permitted the continuity of the vein, essential for future experiments, to remain unimpaired.

The injections were all made at a constant rate, using a pump similar to that described by Woodyatt. This method is very advantageous, since little attention is required for the injection apparatus. The desirability of constant injections depends on the following considerations. (1) The desired changes are brought about gradually without suddenly overwhelming the organism with a great excess of any substance. The injected material is constantly renewed in the blood as it is removed by the tissues, and therefore greater continued changes in blood composition are produced than are possible with single injections. (2) The reaction of the body is equally slowed down, so that it can be studied periodically and more carefully analyzed. (3) With constant inflow of a solution, the organism tends to reach eventually a state of equilibrium, in which conditions which could not be duplicated in any other way may be continued indefinitely. (4) No other method could be used for injections of sugar without diuresis, or any other injection fluid with which the absence of diuresis depends on the disposal of the injected substances by the body, a process which can go on only at a rate not exceeding a certain maximum.

Thompson (2) in an article published in 1900, has drawn conclusions concerning the mechanism of diuresis which there has been little reason to change since. According to him, the diuresis, as measured by the quantity of urine secreted, does not run parallel to the blood pressure, the kidney volume, or the amount of hydremia.

Investigators are unanimous in discarding the general blood pressure as the important element in diuresis. Various assumptions have been made concerning changes in arteriolar or capillary pressure within the kidney, but these still remain outside the realm of experimental proof.

Changes in the blood flow through the kidney have had ardent advocates for this important rôle. Löwi (24) using an extraordinary method, namely, the observation of the color of the venous blood as it emerged from the kidney, came to the conclusion that every diuresis is accompanied by an increased flow of blood. Such an inexact method does not invite great confidence, but Löwi is undoubtedly correct in supporting Thompson in his attack on the oncometric method as an index of blood flow in the kidney. Löwi enclosed the kidney in a plaster cast, making expansion impossible, yet with diuretics there was observed the change in color of the renal vein, to arterial red, that he associated with increased flow. Bunch (25) demonstrated this in the most conclusive manner for the salivary gland, using an air plethysmograph and actually measuring the blood coming from the vein. Stimulation of the chorda tympani gave an increase in the blood flow with simultaneously increased secretion, but with a contraction of the gland. Histological studies of the kidney make it apparent that the renal epithelial cells vary greatly in size under different conditions.

These considerations operate only to cast suspicion on all conclusions as to blood flow drawn from oncometric observations, including those of Starling (26) and Cushny (27) in which the kidney volume was held constant during the administration of diuretic substances. It is interesting to note that in Starling's experiment, where this result is obtained by copious hemorrhage from the carotid, the kidney volume decreased very markedly, a little while after cessation of the withdrawal of blood. A possible interpretation is that the diuretic caused the kidney substance to increase in size. The hemorrhage then had to be much too great in order to keep the oncometer lever stationary, resulting in an actually much diminished flow through the organ. When the cells returned to their normal size, the blood volume was sufficiently reduced to cause the observed oncometric shrinkage. It is not possible here however to do more than hypothesize concerning such experiments and the true solution must wait for new observations in which the blood flow is measured directly.

In this category come the fundamental researches of Bainbridge and Evans (28) and especially of Richards and Plant (29), who perfused the kidney at a known rate with whole blood in a head-heart-lung-kidney preparation. Diuresis occurred from caffeine, NaCl and Na_2SO_4 with absolutely constant blood flow through the kidney.

It therefore seems that one must unavoidably conclude that diuresis can occur independently of changes in blood flow. It is difficult to conceive how changes in the vascular bed, at most changes of 100 per cent or so, can cause increases in urinary secretion amounting to 10,000 per cent or more of the normal, if blood composition is constant or changes in it of no importance. And in addition, changes in blood composition, as has been seen, do occur. The writer believes therefore that the burden of proof should rest on those who claim that blood composition is of less importance in diuresis than renal blood flow.

The secretion from glands in which chemical synthesis is a prominent feature, and which depend almost entirely upon nervous or hormone influences for their regulation is affected to a certain extent by the composition of the blood (Sollmann (3)). The kidney differs from these glands in being concerned almost entirely with the excretion of preformed substances (Tropp (4)) and has no easily demonstrated nervous control. Its prime function is to regulate blood composition. It is assisted in this function by the tissues, which take over injected substances, temporarily in the case of non-utilizable materials, until the kidney is able to dispose of them in due course.

The explanation of events then is fairly complete, with the serious exception that a close chronological relation between changes in blood composition and in urinary secretion has not been demonstrated. Discrepancies occur in every series with which the writer is familiar.

The older writers lay great stress on the concentration of the urine, especially in relation to that of the blood (Frey). It has however been demonstrated that the excretion of various substances reaches its maximum at a different time from that at which the diuresis is greatest, and from this viewpoint, it is much more convenient to assume that each urinary constituent, including water, has its own excretory mechanism, partially, and probably in large degree, independent of the others. The total molecular concentration of the urine would then be only an accidental resultant from the action of these mechanisms. It can then be further assumed with Magnus, that an increase in the concentration of any constituent will cause its excretion in increased amount, and with Sollmann, that the constituents of the blood provide the normal stimulus to renal activity. It is immediately apparent that the independence of the mechanism is not absolute, since one so seldom obtains a great increase in any constituent in the urine without a simultaneous increase in the water, although it is of course possible to do so especially with certain constituents. Water occupies a peculiar position among urinary constituents, since its presence in the renal secretion is necessary not only to relieve the body of an excess, but also to act as a solvent for all the other constituents. It is suggested therefore that the mechanism by which so many salts produce a hydremia is a very necessary one for this purpose. It complicates the picture greatly, however, when explanations are attempted, especially since it makes the content of the body in water and other substances beforehand so important. That this has much influence on diuresis has been shown by Haake and Spiro (30).

But it is further suggested as an amplification of the theory of Magnus, that conversely, a decrease in the concentration of any urinary constituent in the blood tends to decrease renal activity, and may serve to counteract the effect of a simultaneous increase in some other constituent. Thus the simple addition of water to the blood would always bring about such a counteraction by simply diluting the blood, if not compensated in some way, and the bare statement that water given intravenously is not a diuretic, scarcely affords an adequate explanation of the situation. Further, any procedure which caused any substance to leave the blood for the tissues would indirectly diminish urinary secretion.

It is felt that the experiments described in this paper offer some support for this suggestion. The regulatory mechanism of the tissues is evident in the injection of hypotonic NaCl solution, where the chloride and molecular concentration of the blood is kept up to normal, while a hydremia develops, evidently at the expense of the colloid constituents of the plasma, and indicating therefore almost surely an increase in blood volume. The hemoglobin figures also point that way, though their value for that purpose is open to question, through the work of Lamson (31).

The urinary changes, however, do not follow closely those in blood composition. Examination of the tables will show a sort of lag. In the hypotonic NaCl injection, again, hydremia is well developed before any increase in water or chloride output has appeared. Other experiments (Magnus) have shown that diuresis may persist after the water content of the blood has returned to normal.

Two insistent questions, therefore, remain to be answered: First, what is the cause of this lag, and second, should the cause of lag be found to lie within the kidney proper, does diuresis depend on blood composition, according to the suggestions outlined above? In the forthcoming papers of this series, efforts will be made to answer, at least partially, these questions.

SUMMARY

1. Injections of fluid of considerable size have been made intravenously in dogs, according to three methods, without producing diuresis.

2. In such cases definite hydremia and definite hyperglycemia may be present without diuresis.

3. Where hydremia occurs without diuresis, there has usually been a definite decrease in the molecular concentration of the plasma, as shown by the depression of the freezing point (Δ).

4. Solutions of calcium chloride given intravenously cause the urinary secretion to diminish, and in addition precipitate a great loss of water from the blood to the tissues. Given with sodium chloride, calcium chloride will antagonize the diuretic effect of sodium chloride. In such a case, the general blood pressure is not changed.

5. Various observations upon current theories of urinary secretion, and additions thereto, have been made.

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A MODIFIED WOODYATT PUMP

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The pump described by Woodyatt[1] for intravenous infusions at constant rates over long periods of time being so well suited for studies upon diuresis, the principles embodied in it were utilized in a pump made in the machine shop of the Brady Urological Institute for use in such studies.[2] In the course of the design and manufacture of the apparatus, certain modifications were introduced which make it much simpler than the original model, and therefore easier and cheaper to make.

The accompanying photograph shows the principal features. No castings are used, all parts being machined from pieces of brass of various shapes. Motive power is supplied by a small sewing machine motor which can easily be procured anywhere. It is coupled to the shaft of the worm by a small piece of soft rubber tubing of rather thick wall, the worm shaft being made the same size as that of the motor. This makes a simple, flexible, and absolutely satisfactory coupling.

The worm makes 160 revolutions to one of the large disk, this allowing, with the motor used, a maximum pump speed of 55 strokes per minute. Other ratios could be used, depending on the type of work the pump is to perform.

The large disk rests in a plain bearing, lubricated through a suitable oil hole in the disk, in the brass base. Its upper surface bears two small cams which serve to operate the exceedingly simple valve mechanism.

A single post beside the worm is the fulcrum for a long lever actuating the piston. This lever is made to move by a crank pin, which rests in a radial slot in the top of the disk. It is freely movable in this slot, and may be clamped at any point desired by a large thumb screw. This arrangement allows the stroke to be adjusted very precisely at any point between nothing and about 4 cm.

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[1] Woodyatt, Jour. Amer. Med. Assn. '15, lxv, 2067.

[2] Davis, Jour. Urology '17, i, 113.

A crotch at the end of this lever fits over a large pin in a sliding block, which moves in the axis of the pump cylinder. The block bears two arms, and these, with a screw passing through the large pin, clamp the handle of the record syringe which is used as the pump cylinder.

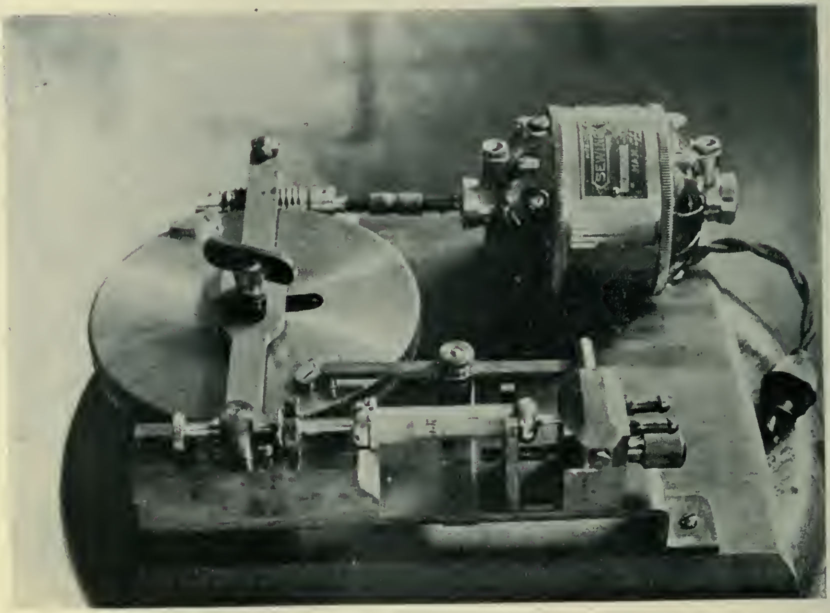

Fig. 1. Photograph of Modified Woodyatt Pump

The piston is shown at the end of the out-stroke, with the valve being changed to the in-flow position.

The tip of the syringe fits into a ground joint in the valve-block, and it is held in place by a yoke fitted with a thumb screw passing through the base of the valve block.

The valve is a simple cylindrical piece of brass, fitting water-tight in a hole bored through the valve block. At the central point of this plunger is a shallow groove, extending clear around which serves to direct the fluid to the proper duct, as the valve moves in and out. The entire valve assemblage can be taken apart, the groove cleaned by wiping it once with a cloth, and put together again in twenty seconds.

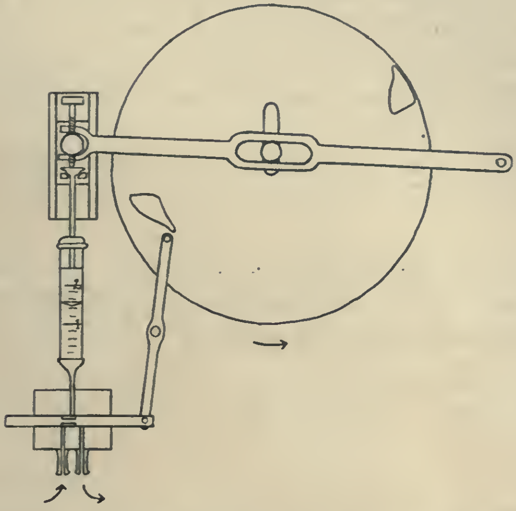

FIG. 2. DIAGRAM OF MODIFIED WOODYATT PUMP

Showing disk, lever, slide, syringe, and valve, but not worm or motor. The diagram is self-explanatory. The piston is shown at the end of the in-stroke, with the valve about to be changed to the out-flow position.

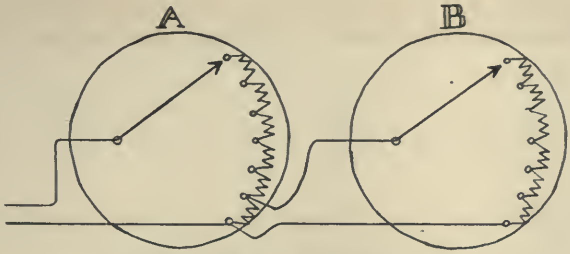

FIG. 3. RHEOSTAT CONNECTIONS

Rheostat *A* gives coarse, and rheostat *B* fine, adjustments.

The valve is operated by a short lever with equal arms, resting on a pivot pin and actuated by the small cams described above.

Variations in speed are obtained by using two of the small rheostats of the type furnished with the motor, connected as shown in the diagram. Rheostat *A* gives coarse, and rheostat *B*, fine adjustments.

The entire apparatus is mounted on a wooden base. It will take a 1 or 2 cc. syringe.

In operation, the instrument has been found eminently satisfactory.

Appreciation is due to Mr. H. I. Hughes, mechanician of the Brady Institute, for the making of the apparatus, and for many valuable suggestions as to its mechanical features.

EXPERIMENTAL NEPHROPATHY IN THE DOG. LESIONS PRODUCED BY INJECTION OF THE BACILLUS BRONCHISEPTICUS INTO THE RENAL ARTERY

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Spontaneous renal lesions are not uncommon in the dog. As a rule they are inconspicuous, but occasionally extensive anatomical changes occur similar, even in their detail, to those found in the human kidney in the progressive, non-suppurative types of nephritis.

The etiology of the disease in the dog is probably more obscure than in man for it has received very little attention. It is immediately evident, however, that the two conditions may result from similar causes. The great majority of chemical irritants already used for the production of experimental renal lesions can have no more place in the etiology of these spontaneous changes in the dogs, than they have in the pathology of the human kidney. Promising experimental results have been obtained recently with bacteria as the exciting agent, and this is in accord with the growing impression that microörganisms may be etiologically associated with the more important types of progressive nephropathies in man.

Assuming this impression to be correct, it is probable that the nephropathy of the dog is the result of some acute infectious disease frequent in the species. Accordingly, in the experiments here recorded, the attempt to produce a progressive nephropathy in the dog similar to those of man, differs in method from the usual procedures, in that a microörganism, the bacillus bronchisepticus, known to produce spontaneous disease in the species, has been employed.

For purposes of comparison the following spontaneous case is described:

Spontaneous case. The animal, a full grown mongrel, was in good general health. Under the influence of paraldehyde (1.7 grams per kilo of body weight) the region of the prostate had been exposed to 112 mgm. of radium bromide for about five hours. The animal recovered from the anesthetic but the next morning it was found dead in the cage

Autopsy. There are no lesions other than those of the kidneys. These are much contracted, and removal of the adherent, thickened capsules shows a coarsely granular surface. On section, the cortex of the kidney is irregularly and markedly thinned; the striations are obscured. The pyramids are somewhat decreased in size and the entire kidney has a pale brownish color.

Microscopic examination shows a good deal of patchy scarring throughout the cortex and upper portion of the pyramids. The scars are dense, infiltrated to a slight extent with mononuclear cells, and the renal parenchyma in these scars shows the usual retrogressive changes. The tubules are greatly dilated, except in the scarred areas, where they are very small with low epithelium, and may contain casts or cellular detritus. The dilated tubules are lined by a high columnar epithelium which shows considerable vacuolation. Their lumina contain granular detritus and an occasional cast. The glomerili are enlarged; in some places they appear more numerous, in others less frequent than normal. None of them appears entirely normal. The glomerular capsules are delicate, except in the scarred areas. The glomerular spaces are large. They contain serum and occasionally mononuclear cells. The tufts are swollen, very cellular and show varying changes including hyaline thrombi, partial or complete hyalinization, intercapillary adhesions, and adhesions between the tuft and capsule. The blood vessels, except in the scarred areas, do not seem to be markedly affected. The tubules, in the upper portion of the pyramids especially, are dilated and irregularly tortuous; their epithelium is, for the most part, cubical and in some places seems to be stratified. Occasional tubules are found, so irregular in shape that they must have been formed by a rupture of the separating wall between several adjoining tubules (see figs. 1 and 2).

METHOD

The organism used for injection corresponded in its microscopical characteristics, staining qualities, cultural reactions and pathogenicity for lower animals to the bacillus bronchisepticus.

About 5 cc. of either a thirty-six to forty-eight hour growth in litmus milk or of an emulsion of a growth from an agar slant in sterile salt solution were injected directly into the renal artery. At first both, later only one kidney was injected. The remaining one was subsequently similarly injected, or removed after the acute symptoms following the initial procedure had subsided.

All operations were done under ether anesthesia and with complete surgical asepsis.

The kidney was reached by a longitudinal abdominal incision usually about 10 cm. long and 1 cm. from the middle line, through which the intestines were withdrawn from the abdomen and covered with towels. By lifting the kidney from its bed, and using gentle, blunt dissection, it was possible to isolate the renal artery without trauma to its accompanying nerves. The culture was introduced directly into the artery by a fine, bent hypodermic needle, after temporary interruption of the blood stream by a serre-fine. After injection, the vein was compressed for a few seconds, subsequent to the release of the arterial circulation, in order to secure complete spread of the bacterial emulsion throughout the kidney. The kidney was then readjusted in its normal position, the intestines replaced, and the abdomen carefully closed in layers by silk.

As will be seen from the protocols, the immediate results of this procedure varied markedly. Some of the animals showed definite generalized distemper, with conjunctivitis, nasal discharge, anorexia and loss of weight. Their urine at first contained some blood and showed large amounts of albumen. On the other hand, other dogs showed no signs whatever of general infection, and after the first few days, only the slightest traces of albuminuria. The larger number of animals reacted to the injection definitely, but without the severe generalized infection of the first group. It seems reasonable to explain these results on the ground of variation in susceptibility of the different animals. The severe, overwhelming infections occurred as a rule in young dogs, while those showing practically no reaction were old, or had at least attained their full growth. This coincides with the well-known immunity which commonly follows an attack of distemper.

It is possible, therefore, to divide the animals into three groups.

(1) Immune animals that showed only a transient renal lesion and no general reaction.

(2) Animals that died acutely with a fulminating renal lesion and an acute general reaction.

(3) Those which showed a milder renal lesion which progressed after the less severe general reaction had subsided. In this last group the animals ultimately succumbed to renal insufficiency, provided the uninjected kidney was removed shortly after the acute stage had passed.

A protocol, illustrative of each of the above groups, has been selected from a large number and is presented below.

Group I

Immune animals that showed only a transient renal lesion and no general reaction.

Illustrative case. Dog 27, a full-grown male.

On March 18, 1916, under ether anesthesia, a laparotomy was performed and 5 cc. of a milk culture of b. bronchisepticus was injected into the right renal artery. The animal recovered from the operation promptly. On March 21 the urine contained a moderate number of casts, small round cells, and 1 gram of albumen to the liter (Esbach).

The urinary changes persisted; on March 24, 200 cc. of slightly cloudy urine obtained by catheter showed a specific gravity of 1031, albumen 0.5 gram per liter, and many casts and cells in the sediment. Under ether anesthesia, the abdomen was again opened and the lower third of the uninjected left kidney resected. The right kidney was found much enlarged, with injected capsular vessels and mottled surface. A wedge-shape piece was resected for histological examination.

Section of kidney six days after injection. The capsule of the kidney is uniformly thickened by a very vascular granulation tissue which is replacing an exudate of serum, red blood cells, and relatively few polymorphonuclear leucocytes. This inflammatory process extends into the renal parenchyma only in focal areas, and here the interstitial tissue shows great engorgement of the capillaries, infiltration with mononuclear cells and occasionally polymorphonuclear leucocytes. In such areas the tubules may be either dilated or collapsed; their epithelium may be flat, cylindrical or vacuolated and occasionally regenerative processes may be seen (fig. 3). The glomeruli, likewise are involved. The tufts are swollen and fill the capsular space. The capsules themselves are delicate. The tufts show occasional extensive hyaline thrombi (fig. 4) and intercapillary as well as capsular adhesions. Occasionally red blood cells or polymorphonuclear leucocytes may be found in the capsular space. In these scarred areas the finer architecture of the kidney is obscured, while between the scars changes of interstitial tissue, tubules and glomeruli are not remarkable.

The important points in the history of the animal subsequent to thesecond laparotomy are indicated in Chart I.

On April 26, thirty-eight days after the original injection of b. bronchisepticus into the right renal artery and three weeks after the removal of the left kidney, the animal was anesthetized and a small wedge of the right kidney was excised. It showed the following histological picture:

The capsule is thickened, but otherwise shows no evidence of active inflammatory process. Extending into, and scattered through the cortex, are occasional typical scarred areas where the interstitial tissue is increased and studded with small mononuclear cells. Here the tubules are atrophied or dilated, and lined by a low cubical epithelium. They may contain casts. The glomeruli are numerous in these scars; they vary greatly in size and show capsular adhesions, and early hyalinization. The remainder of the kidney cortex including the blood vessels presents no definite change (fig. 5).

The general condition of the animal and the urinary findings immediately after the fourth operation are presented in Chart II.

During the next two months the dog was given systematic daily exercise on a treadmill. He remained in excellent condition. The urine showed either no albumen, or only traces, and rarely an occasional cast.

On July 27, about four and one-half months after the original injection of b. bronchisepticus into one kidney and more than three months after total removal of the uninjected kidney, the mean blood pressure was 140 mm. Hg., the phenolsulphonephthalein excretion 49 per cent in one hour, and the blood urea 48 mgm. per 100 cc.

CHART I

Dog 27

DATE	URINE				REMARKS
	Amount	Specific gravity	Albumin, gram per liter	Microscopic examination	
	cc.				
March 25					Looks well but does not eat.
March 29	340	1022	0.25		Has made a good recovery.
March 30	450	1030	0.5		
March 31	450	1030	0.25		
April 1	400	1040			
April 2	420	1040			
April 3	250	1020			
April 4	200	1032			
April 5	450+	1032	0.25	Negative.	Animal is in excellent condition. Third operation. Under ether anesthesia the left kidney was removed through a lumbar incision.
April 6					Dog has made an excellent recovery.
April 7	400	1020	Trace		Phenolsulphonephthalein output 30 per cent in one hour. Blood urea 22 mgm. per 100 cc.
April 8	350	1028	0.25		
April 9	450	1032			
April 10	440	1034			
Aptil 11	240	1036	0.25	Casts, plus few mononuclear cells.	Blood urea 30 mgm. per 100 cc.
April 12	350	1040			
April 13	460	1030	0.25		Phenolsulphonephthalein output 52 per cent in one hour. Blood urea 25 mgm. per 100 cc.
April 14	450	1020	Trace		
April 15	450	1020			
April 16	250	1030			
April 17	450	1030			
April 18	150	1030			
April 19	400	1040	0.25		Phenolsulphonephthalein output 50 per cent in one hour. Blood urea 27 mgm. per 100 cc.
April 20	600	1021			
April 21	650	1022			
April 23	220	1040			
April 24	220	1040			
April 25	140	1040			
April 26					Mean blood pressure is 120 mm. Hg.

CHART II

Dog 27

DATE	URINE				REMARKS
	Amount	Specific gravity	Albumin, gram per liter	Microscopic examination	
	cc.				
April 26	340	1054			
April 27	440	1020			Excellent recovery.
April 28	250	1030	0.5		
April 29	300	1042			Phenolsulphonephthalein output 46 per cent in one hour. Blood urea 30 mgm. per 100 cc.
April 30	410	1034			
May 1	440	1034			
May 19			0.25	Pus. No casts. A rare renal cell.	Phenolsulphonephthalein output 69 per cent in one hour. Animal very well.
May 22	450	1050			
May 23	350	1030			
May 24	440	1032			

DISCUSSION

The above protocol is representative of a group of older dogs in which no demonstrable general infection occurs after the injection of the bacillus bronchisepticus into a renal artery. The kidney, however, shows immediate acute focal inflammatory lesions which rapidly subside and result in focal scars similar to those that are frequently encountered both in the canine and human kidney. These latter lesions are associated with an intermittent albuminuria and cylindruria which persist for months, although there are no other evidences of renal insufficiency.

Group II

Animals that died acutely with fulminating renal lesion and an acute general reaction.

Illustrative case. Dog. 17. Large young male.

February 29, 1916. Under ether anesthesia a laparotomy was performed and 5 cc. of a milk culture of b. bronchisepticus injected into the right renal artery. Immediately after the injection and release of the arterial circulation the organ became unusually tense and firm and the needle puncture in the artery wall bled considerably.

The next day the blood urea was 122 mgm. per 100 cc. The animal developed diarrhoea, anorexia, and oliguria, and death occurred on the sixth day after injection.

Autopsy. The right kidney is at least one-half larger than the left (figs. 6 and 7). Its capsule is not adherent, though somewhat thickened and suffused with blood. The surface of the organ is brownish purple, thickly mottled with yellowish, raised areas from 1 to 2 mm. in diameter. On section the kidney is purplish red, engorged with blood, and with all the normal markings obscured. No evident abscesses are present. Cortex and medulla seem to share equally in the increase in size of the kidney. The rest of the organs present nothing remarkable.

Under the microscope masses of red or white blood cells are scattered through fairly well preserved kidney tissue (fig. 7). The interstitial tissue is spread by engorged vessels, edema and cellular accumulations. In many places the exudate is composed almost entirely of red cells; in others of polymorphonuclear leucocytes. These areas give the section a mottled appearance. In the areas of greatest engorgement the architecture of the kidney is lost. Collapsed or nearly collapsed tubules, lined by low epithelium, streak the mass of red and white cells. The tubules themselves contain in these places small clumps of cellular detritus. Where the tubules are better preserved the same exudate occurs in the interstitial tissue to a lesser extent. The tubular epithlium shows acute and vacuolar degeneration. The glomeruli are involved in most instances. They may show simply a compression, but as a rule, emboli occur, associated with necrosis of part (fig. 9) or all of the tuft, and even with miliary abscess formation (fig. 10). Where the process is less marked in the tuft, a wedge of necrotic capillaries appears plastered to the capsule. The capsular space may contain red blood cells and polymorphonuclear leucocytes. The capsule itself, except where it is in contact with the diseased tuft, is uninvolved. The large blood vessels are obscured by the extensive exudative process. In the pyramids the collecting tubules contain hyaline casts, cellular detritus, red blood cells, and polymorphonuclear leucocytes.

Sections of the uninjected kidney and of other viscera show only an extreme degree of cloudy swelling.

DISCUSSION

The above protocol represents a large group of young animals where the injection was followed by a fulminating acute non-suppurative infiltration process. It is probably focal in nature, but the foci are so large and so numerous that the intermediate areas are only demarcated by a slightly less intense involvement. Such lesions are rare in human pathology, but they find their analogy in occasional cases of acute septicaemia with or without cardiac valvular involvement.

Group III

Animals with a milder renal lesion which progressed after the less severe general reaction had subsided.

Illustrative case. Dog. 25. March 10, 1916. Under ether anesthesia a laparotomy was performed and 5 cc. of a milk culture of b. bronchisepticus injected into the right renal artery. The animal recovered from the operation promptly. It was drowsy and ate little for several days, and after these mild general signs had disappeared, the urine continued abnormal as indicated in Chart III. The animal was lively and seemed well. Although he ate abundantly there was definite loss of weight. On March 28 under paraldehyde anesthesia (1.7 cc. per kilo of body weight) each ureter was exposed and cannulated. The output of urine from the left kidney in one hour was 45 cc. and contained 17 per cent phenolsulphonephthalein, while from the right it was 15 cc. and contained only traces of the dye.

During the night the dog died, not having definitely recovered from the anesthetic and operation.

Autopsy. The right kidney is not markedly decreased in size (fig. 11). The capsule is thickened and adherent. The surface is slightly granular and pale reddish-brown. On section the cortex is slightly narrowed and its striations are obscured. The pyramids are paler than the cortex. The pelvis is normal. The remainder of the autopsy reveals no noteworthy changes.

On microscopic examination there is no appreciable difference between specimens removed twelve days after injection and those of the autopsy, which was on the eighteenth day. The capsule is irregularly thickened by fibrous tissue which shows no evidence of active inflammatory process. The cortex of the kidney is greatly changed by an

CHART III

Dog 25

DATE	URINE				REMARKS
	Amount	Specific gravity	Albumin, grams per liter	Microscopic examination	
	cc.				
March 16	260		2.0	Many epithelial cells.	
March 18	330	1022	2.0	Casts; few small round cells.	
March 19	450	1018			
March 20	250	1022	0.5	No casts seen.	
March 21	370	1020	0.5		Phenolsulphonephthalein excretion 40 per cent in one hour. Blood urea 100 grams per 100 cc.
March 22	660	1012	2.0		Ether anesthesia, laparotomy. The left kidney was found normal. Its lower pole was resected. The right kidney was definitely enlarged and of much firmer consistency than normal. The surface was somewhat mottled.
March 23	100	1032	6.0	Casts, blood and small round cells	Animal's condition good. Wound healing well.
March 25	450	1012	0.5		
March 26	350	1016			
March 27	200	1030	2.0		
March 28	250	1022	1.0		

infiltration of mononuclear cells throughout the interstitial tissue (fig. 12). This infiltration is not uniform. In many places it forms dense masses which compress and obscure the tubular parenchyma. These tubules contain casts and occasional masses of necrotic cells, but almost always retain a low, cubical, well preserved epithelium. Where the tubules are not so markedly compressed, they likewise contain foreign elements in their lumina, and a higher vacuolated epithelium which, in many places, shows regenerative mitosis (fig. 13).

Throughout the cortex the glomeruli are very conspicuous. They are all enlarged, relatively acellular and stain pale pink in contrast to the deep blue-streaked cortex. They contain little blood. The glomerular capsule is surrounded by mononuclear cells similar to those in the remainder of the interstitial tissue. Otherwise the capsule is delicate. The glomerular space is usually well defined and may contain occasional blood cells, polymorphonuclear leucocytes, or serum. The glomerular tuft in many places shows hyalinization and accumulations of polymorphonuclear leucocytes. Furthermore, adhesions between tuft and capsule occur, although not very frequently (fig. 14). The larger blood vessels show a definite thickening of the walls, which apparently involves both intima and media, although the latter to a more marked degree (fig. 15). The left uninjected kidney shows a few areas of interstitial infiltration with small mononuclear cells.

DISCUSSION

The above experiment approximates in its histological results more nearly the chronic progressive renal lesion found spontaneously in the dog. However, since this animal was sacrificed in the attempt to study the differential function of the two kidneys, a second case of the group may be presented to illustrate more clearly the progressive nature of the lesion.

Illustrative case No. II. Dog. 19. On March 1, 1916, under ether anesthesia a laparotomy was performed and 5 cc. of a milk culture of b. bronchisepticus was injected into the right renal artery. During the subsequent week the animal seemed entirely well. The urine contained a slight trace of albumen; the phenolsulphonephthalein output in one hour was 50 per cent.

A second laparotomy on March 9 showed the right kidney surrounded by rather numerous adhesions which bound it to the head of the pancreas. It was somewhat enlarged, and its surface was deep red, with fine yellowish mottlings. A small wedge was excised for microscopic examination.

Microscopic examination of kidney nine days after injection. The capsule is irregularly thickened by vascular granulation tissue. The cortex of the kidney is uniformly changed. The interstitial tissue is increased and appears as a loose, young, connective tissue stroma which does not compress the parenchyma of the cortex to any extent (fig. 16). The tubules are indistinctly made out on account of the very extensive epithelial necrosis which has everywhere taken place. In most instances the epithelium of the convoluted tubules lies free within the lumen, and appears as a pale pink-staining cast. There is, however, a low epithelium to be seen in the collecting tubules, and some evidence of early degeneration in the convoluted ones (fig. 17). The glomeruli vary greatly in appearance. Many of them show extensive vacuolization, with the walls of the tuft spread wide apart, and plastered in many places to the capsule. Others show marked increase and swelling in the cellular elements of the tuft. Still others are engorged, and cells, as well as serum, may fill the glomerular space (fig. 18). The glomerular capsules are involved in the same process described in the interstitial tissue elsewhere. They show a slight increase of loose connective tissue at their peripheries. There are no marked changes in the blood vessels.

The animal recovered rapidly from this second operation. On March 15 the urine contained only the slightest trace of albumen; the sediment was negative.

Chart IV indicates the further progress of the disease.

Autopsy. All the organs are normal except the right kidney which is surrounded by some adhesions; it is small and shrunken in appearance and weighs only 6.5 grams (fig. 19). There is no evident cardiac hypertrophy.

Microscopic examination of kidney removed at autopsy fifty days after injection.

The entire capsule is thickened by fibrous tissue. The cortex is irregularly involved by the chronic inflammatory process (fig. 20). In the areas most markedly involved the fibrous tissue is dense and has caused an almost complete disappearance of the tubules. Most of them have minute lumina and a very low epithelium, others have very large lumina containing a pink-staining, albuminous material. In the more extensively scarred areas the glomeruli are still abundant and conspicuous on account of absence of the tubules. They vary from very small ones to those several times the normal size, and show all stages of necrosis, healing with adhesion formation, and hyalinization (fig. 21). The blood vessels in these densely scarred areas have somewhat thickened walls, although this is not conspicuous. In nearby

CHART IV

Dog 19

DATE	URINE				REMARKS
	Amount	Specific gravity	Albumin, grams per liter	Microscopic examination	
	cc.				
March 18	220	1042	0.5		
March 19	260	1040	4.0		
March 20	250	1035	1.0	Many casts.	
March 21	120	1035	0.25	Occasional cast.	
March 22	40(?)	1045	4.0		Phenolsulphonephthalein 50 per cent in one hour. Blood urea 48 mgm. per 100 cc. Animal has marked general infection and is sick.
March 23	150	1020	2.0		
March 24	150	1038	1.5	Occasional cast.	Animal is better, but does not eat.
March 25	110	1040	1.5		
March 26	200	1035	0.5		
March 28	140	1020	0.25		Much better; eats and walks. Nose and eyes are almost clear.
March 29	450	1010	Trace		
March 30	460	1010	0.25		
March 31	450	1010			
April 4	450	1008	Trace		
April 6	420	1012	0.25		
April 7	450	1012	0.25		Operation. Left nephrectomy.
April 8	200	1010			
April 9	140	1012			
April 10	150	1012			
April 11	290	1012	0.5	Few casts; much pus; occasional epithelial cell.	Phenolsulphonephthalein output a trace in one hour. Blood urea 114 mgm. per 100 cc.
April 12	140	1012			
April 13	260	1022	0.5		Phenolsulphonephthalein output a trace in one hour. Blood urea 186 mgm. per 100 cc.
April 14					Vomits. Urine cloudy. Blood urea 358 mgm. per 100 cc.
April 15	75	1017	2.0		
April 17	250	1010	2.0		Vomits, drowsy, condition poor. Blood urea 348 mgm. per 100 cc.
April 18					Death.

areas the changes are less extensive but have the same general characteristics. The tubules in particular are of interest on account of their increased size and the very high, extensively vacuolated epithelium which lines then.

The uninjected kidney, removed thirty-eight days after initial operation, shows an occasional area of small, round cell infiltration of the interstitial tissue with an associated dilation of the tubules and an atrophy of their lining epithelium. These extend along the course of the blood vessels, which have somewhat thickened walls. No glomerular changes are to be seen.

DISCUSSION

The above two protocols of Group III are characteristic of the changes found in a number of animals subsequent to the injection of b. bronchisepticus into the renal artery. The definite evidences of general infection were associated with and followed by acute renal changes which in part subsided with resultant gross and histological changes typical of those found spontaneously in the dog and in the better known small granular kidney of chronic diffuse nephritis in man.

The initial acute changes in the kidney were so severe that they resulted in rapid and extensive anatomical alteration of the renal cortex together with impairment of its function so that death from renal insufficiency occurred shortly after the removal of the uninvolved kidney.

CONCLUSIONS

Spontaneous renal lesions, similar even in detail to those found in the human kidney in the progressive, non-suppurative types of nephritis, occur in dogs. A similar condition may be experimentally produced by the injection of the bacillus bronchisepticus into the renal artery of dogs.

The results of this injection vary, but the animals tend to group themselves as follows:

1. Those in which no demonstrable general infection occurs; the kidney, however, shows immediate acute inflammatory lesions which rapidly subside and result in focal scars associated with intermittent albuminuria and cylindruria.

2. Those that died acutely with a fulminating renal lesion and an acute general infection.

3. Those in which there was definite evidence of general infection as well as renal involvement. The first subsided while the kidney changes progressed, and led so rapidly to functional impairment that the organ was unable to maintain its efficiency after the other kidney had been removed.

EXPLANATION OF PLATES

Spontaneous Renal Lesion

Fig. 1. The cortex of the kidney shows patchy scars infiltrated with mononuclear cells, glomerular adhesions and dilated tubules.

Fig. 2. Is an enlargement from figure 1 and shows the glomerular and tubular changes in detail.

Group I. Animals that showed only a transient renal lesion following the injection of b. bronchisepticus into the renal artery.

Fig. 3. Shows the acute diffuse capsular and the focal cortical inflammatory reaction present in the kidney six days after injection of the renal artery.

Fig. 4. A glomerulus from figure 3 enlarged to show the hyaline thrombus in the tuft.

Fig. 5. Section of the same kidney represented in figures 3 and 4 thirty-two days later. The capsule is thickened and focal scars are scattered through the cortex.

Group II. Animals that died acutely with a fulminating renal lesion and an acute general reaction.

Fig. 6. *A*. Actual size and appearance of the right kidney at autopsy six days after injection of b. bronchisepticus into the right renal artery.

B. The left kidney of the same animal.

Fig. 7. A second example of this group. The reaction is somewhat less severe.

Fig. 8. Fairly well preserved kidney tubules spread apart by masses of red and white blood cells.

Fig. 9. Emboli in the capillary tuft, necrosis and hemorrhage into the capsular space.

Fig. 10. Miliary abscess of a glomerulus.

Group III. Animals which showed a milder immediate renal lesion which progressed after the general reaction had subsided.

Fig. 11. *A*. Actual size and appearance of right kidney at autopsy eighteen days after the injection of b. bronchisepticus into the right renal artery.

B. The left kidney of the same animal.

Fig. 12. Diffuse mononuclear infiltration throughout the renal cortex.

Fig. 13. An enlargement from figure 12, shows mononuclear infiltration of the interstitial tissue, dilatation of the tubules and degeneration of their epithelium.

Fig. 14. An enlargement from figure 13, shows a characteristic glomerular adhesion.

Fig. 15. Shows the accumulation of mononuclear cells around the larger blood vessels.

Fig. 16. Is taken from a section of kidney nine days after injection of the renal artery. The capsule shows an extensive subacute reaction. The tubular, glomerular and interstitial tissues are represented in the following two figures.

Figs. 17 and 18. The epithelium of the convoluted tubules is necrotic, the interstitial tissue infiltrated with mono- and polynuclear cells, the glomerulus greatly swollen and infiltrated with cells.

Fig. 19. *A*. Actual size and appearance of right kidney removed at autopsy fifty days after injection of renal artery.

B. Left kidney of same animal for comparison. There is a slight compensatory hypertrophy.

Fig. 20. (Compare with figure 16.) A section of the kidney fifty days after injection. It shows a fibrous capsule, diffuse scarring of the cortex and tubular and glomerular changes as shown in figure 21 and figure 22.

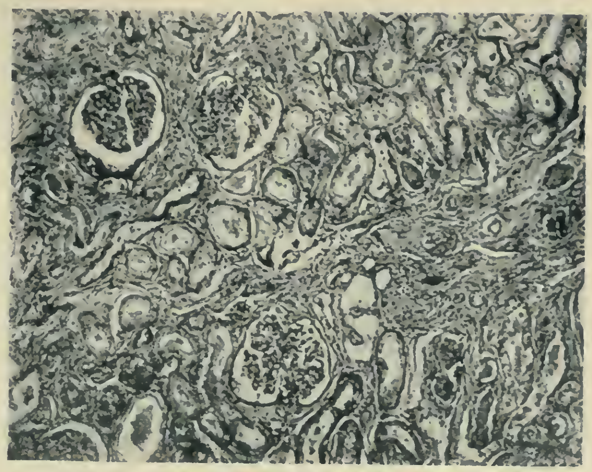

FIG. 1

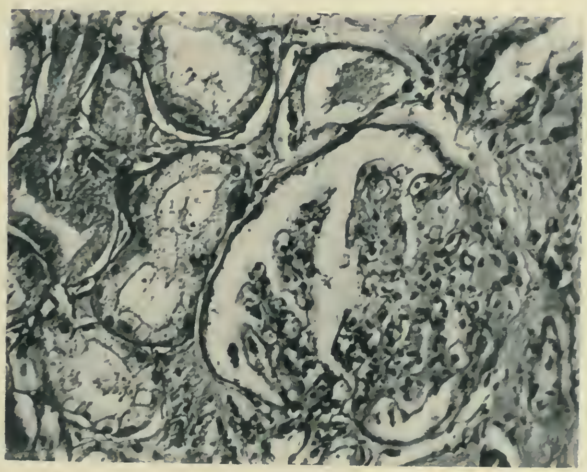

FIG. 2

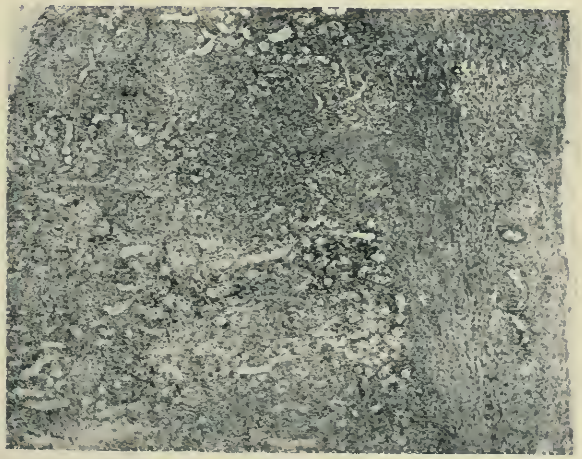

FIG. 3

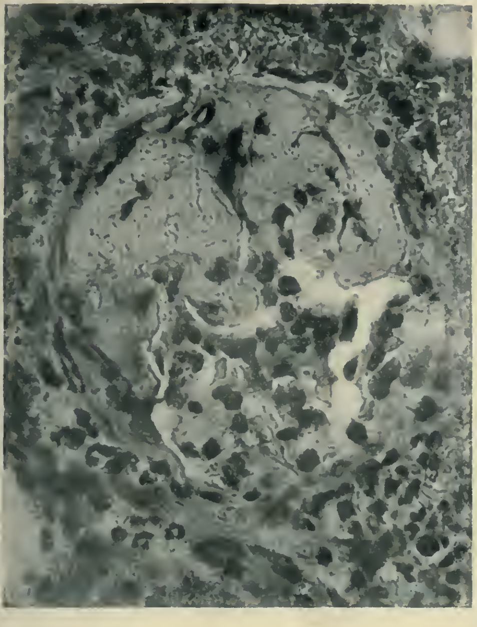

FIG. 4

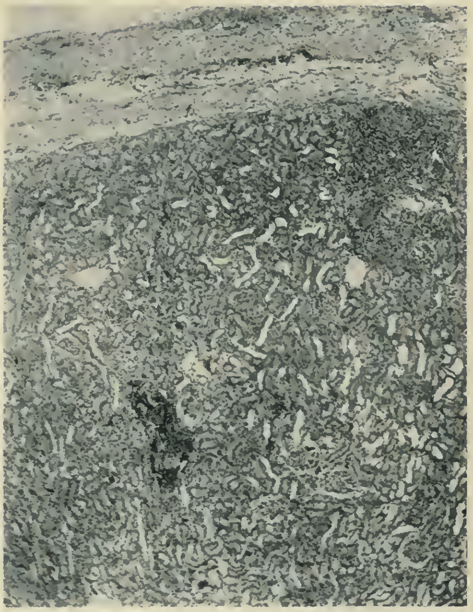

FIG. 5

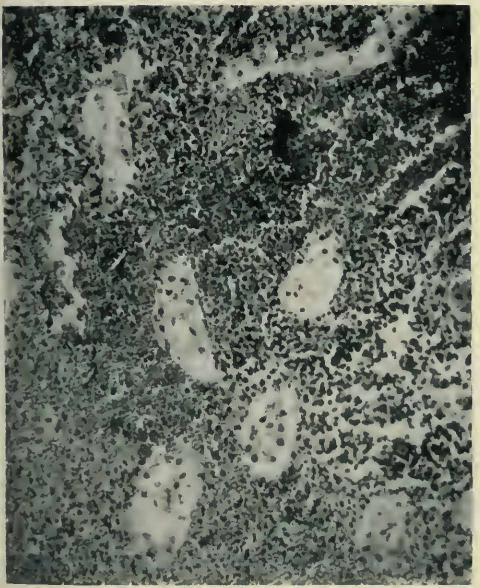

FIG. 8

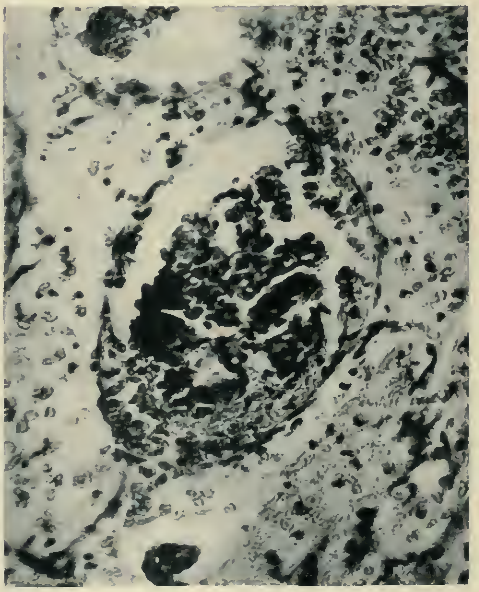

FIG. 9

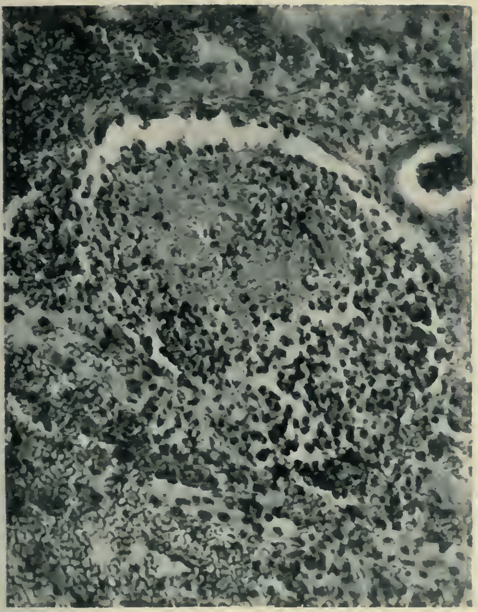

FIG. 10

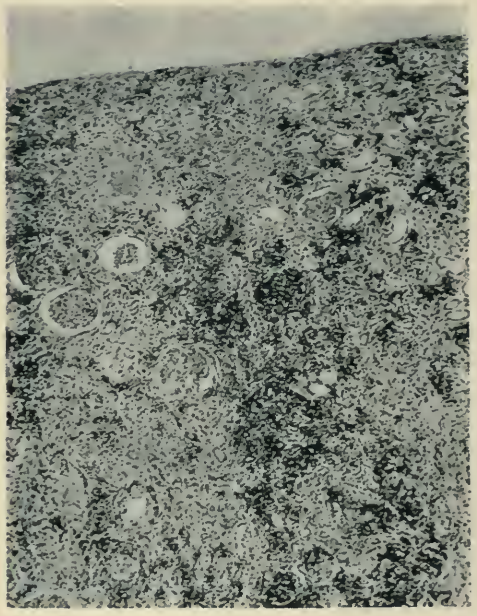

FIG. 12

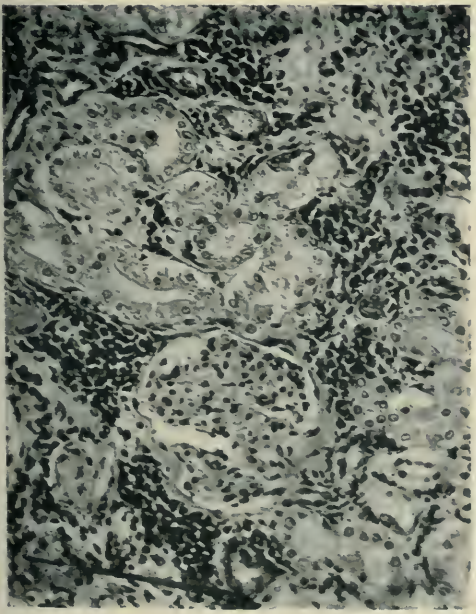

FIG. 13

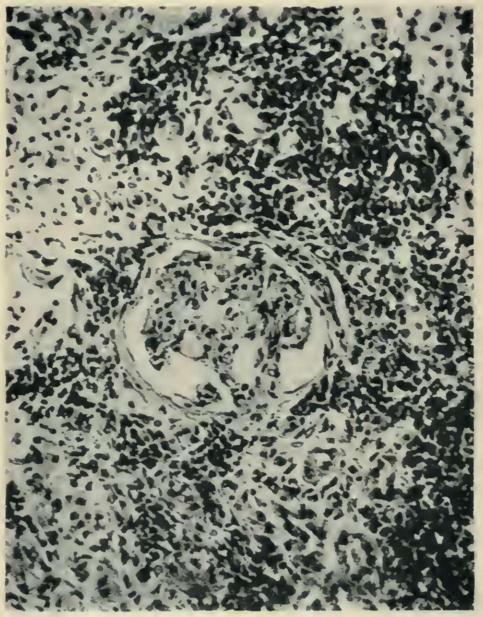

FIG. 14

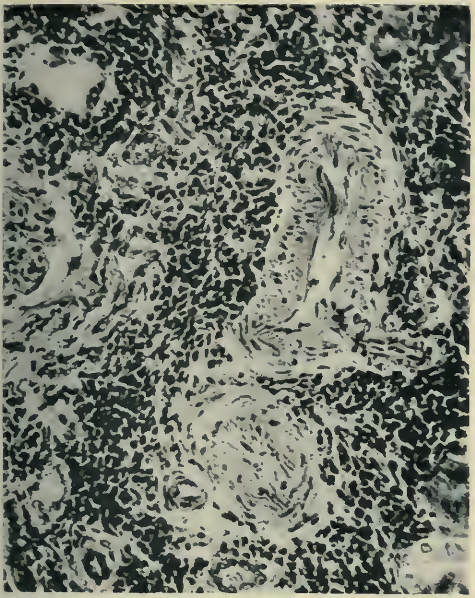

FIG. 15

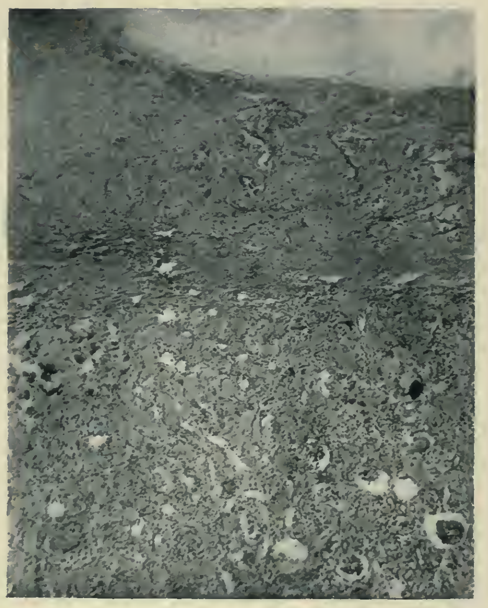

FIG. 16

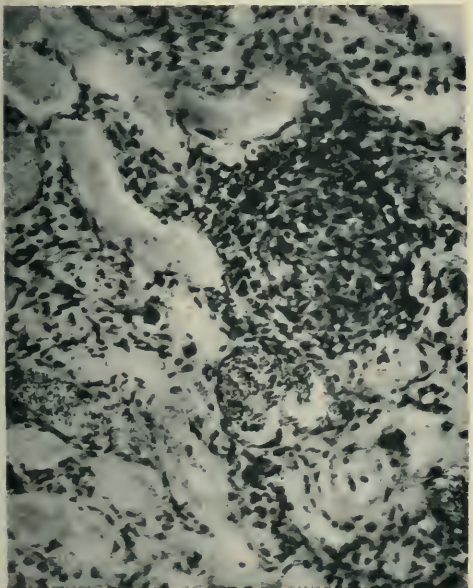

FIG. 17

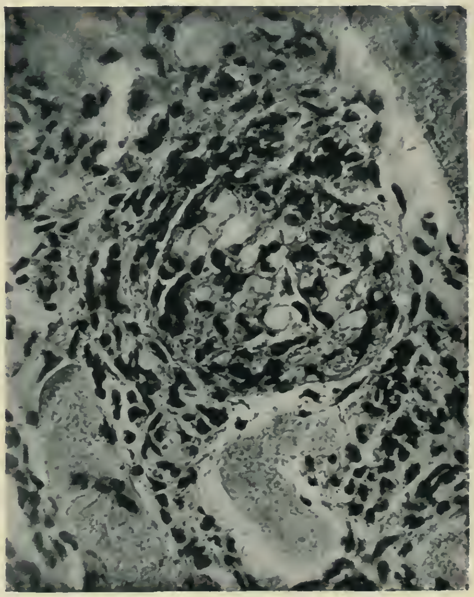

FIG. 18

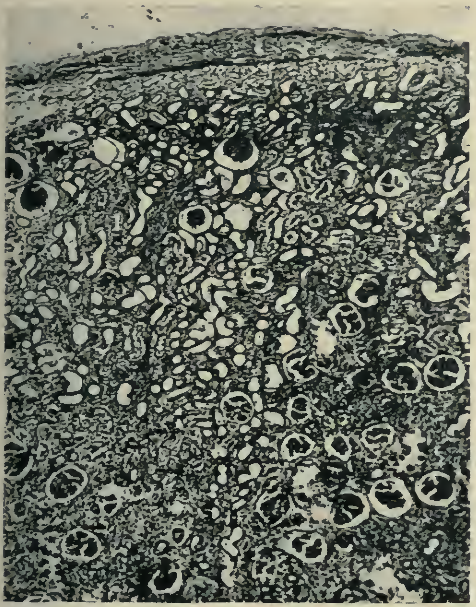

FIG. 20

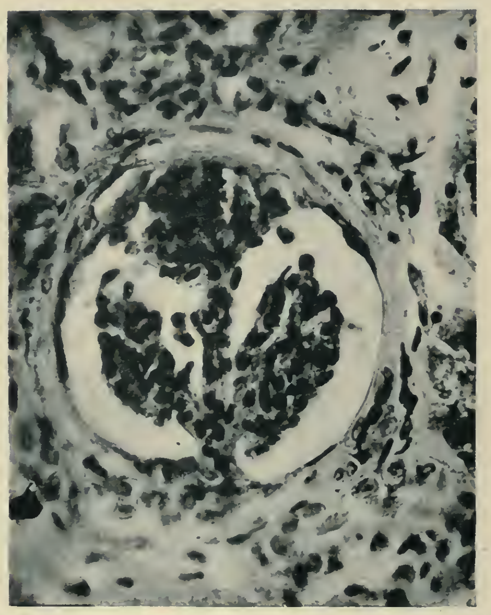

FIG. 21

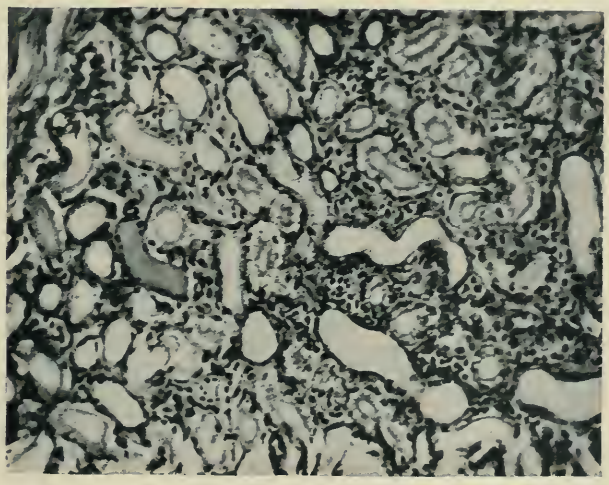

FIG. 22

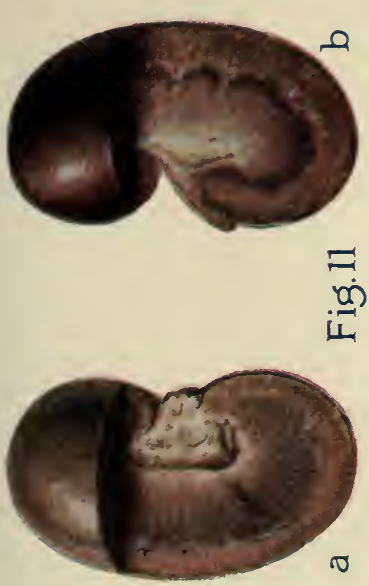

Fig.11

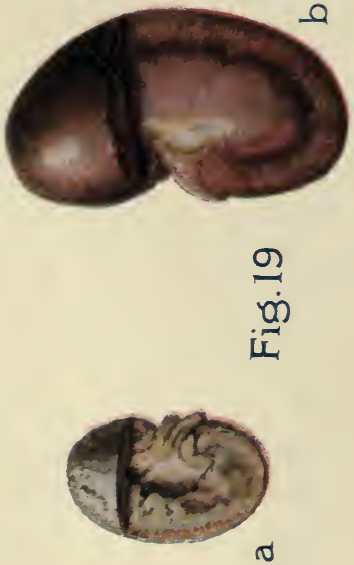

Fig.19

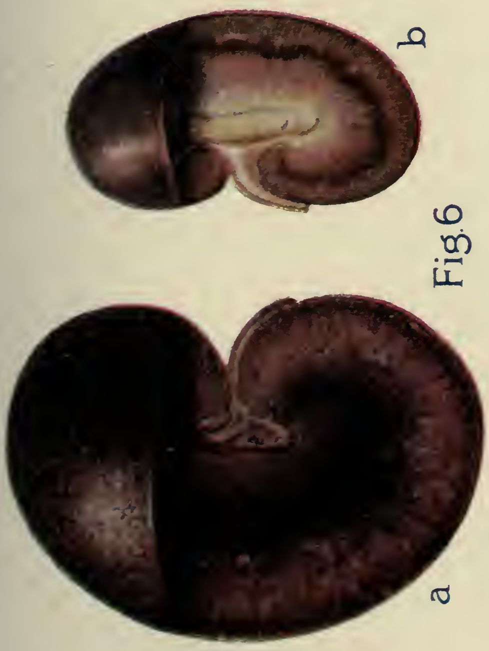

Fig.6

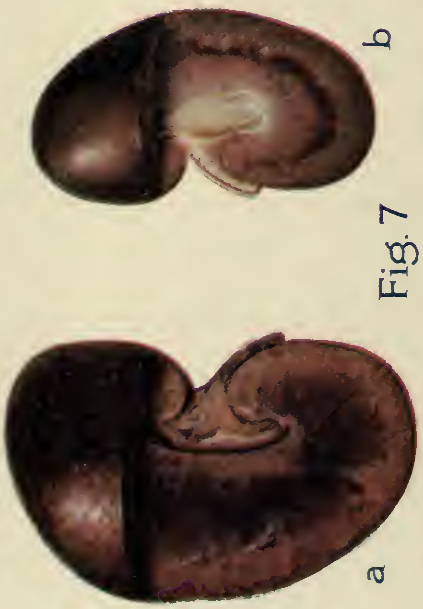

Fig. 7

Wm. P. Didusch

A CASE OF MULTIPLE MYELOMATA WITH CHRONIC NEPHRITIS SHOWING BENCE-JONES PROTEIN IN URINE AND BLOOD SERUM

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Since the description in 1848 by Bence-Jones and MacIntyre (1) of a case of "Mollities Ossium" with a peculiar urinary protein and "gelatiniform tumors of vertebrae and ribs," over a hundred cases have been recorded presenting either or both features of this unusual syndrome. Von Rustizky (2) in 1876 first employed the term "multiple myelomata" in describing the condition and the appellation has persisted, although, as Collins says, rather because of the situation of the tumor than on account of a uniform histogenesis.

The literature of multiple myelomata and allied conditions has been reviewed thoroughly by Jellinek (3), Menne (4), and Simon (5) and more recent cases have been summarized by Vance (6), so that it is not necessary to make an exhaustive review of this subject in the present paper.

The disease can still be considered a rarity although its frequency in recent years has increased. In the present instance, however, several unusual complications make it especially noteworthy, among them is the fact that this is probably the first case in which definite clinical evidence of advanced nephritis has been associated with retention of a large measurable amount of the Bence-Jones protein in the circulating blood.

The patient was a Chinaman, aged 63 years, admitted to the New England Baptist Hospital, September 10, 1916, house service of Dr. George S. C. Badger, and seen in consultation by Dr. Harry W. Goodall and Dr. Loring T. Swaim. He complained at that time of having had a stiff and painful back for three months and of loss of weight and strength. Physical examination showed stiffness of the entire spine and pain in the lower lumbar and sacral region. His haemoglobin was 35 per cent, red blood cells 2,600,000; blood smear showed considerable achromia, many small forms, but no abnormal leucocytes. The urine was clear, pale, specific gravity 1016, acid, "albumose" 1 per cent, no sugar. There was a copious precipitate at about 60°C., largely clearing on boiling but not reappearing with cooling. The precipitate formed with concentrated HNO_3 largely cleared with boiling and reappeared on cooling. The sediment contained a rare hyaline cast. Roentgen examination by Dr. Morrison, showed evidences of hypertrophic changes of the lumbar spine and sacro-iliac joints; a destructive process in the crest of the right ilium and sacro-iliac joint, suggestive of carcinomatous involvement; and a somewhat similar process on the left. The patient was discharged unrelieved from the New England Baptist Hospital to the Peter Bent Brigham Hospital on November 11, 1916, with the diagnosis of multiple myelomata.

On admission to the Peter Bent Brigham Hospital (Med. No. 5581) his past history was found to be essentially negative. Ten months before admission he had had an attack of coryza which lasted four weeks. Six weeks later he had a severe, sudden pain in the lower back radiating down both legs. This persisted with several remissions for about five weeks, most marked when he walked. He grew progressively weaker after the attack of coryza. Six months ago he had a sudden, severe pain in the left shoulder and the chest became acutely painful. This was followed in a few days by a similar condition in the right chest. Breathing was very painful and a slight cough added much to the irritation. Two months ago all his pains became so severe that he was unable to move from bed. During the last ten days previous to entrance he vomited unstained food material five or six times a day, usually without nausea. He lost considerable weight in the last ten months.

Physical examination on November 11, 1916, shows an anaemic, pasty-looking Oriental, lying in bed, every slightest movement causing expressions of acute pain. His mucous membranes are pale. The heart is slightly enlarged to the left; a systolic bruit is heard over the entire precordium, most intense at the mitral area. The thorax is asymmetrical with a bulging of the ribs in the right back with right dorsal scoliosis. The right chest and back show diminished resonance with bronchial breathing and many fine and coarse râles. The left chest shows similar signs though less marked. The ribs on both sides are tender, with nodosities, defects, and fractures easily demonstrable in many of them. The spine is held rigid with marked tenderness over the sacrum and lower lumbar region. The left shoulder muscles are spastic; left supra-scapular region is distinctly tender. The blood pressure is 116 systolic; 60 diastolic. The reflexes are much exaggerated; a double ankle clonus is present.

On admission the blood examination was as follows: white blood corpuscles 9800; red blood corpuscles 2,384,000; hemoglobin 32 per cent; color index 0.66. Differential count—250 cells; polymorphonuclears 76.5 per cent, lymphocytes 11.7 per cent, large mononuclears 9.6 per cent, eosinophiles 1 per cent, myelocytes 1 per cent. The red blood cells show marked stippling, achromia and anisocytosis. No nucleated forms are seen.

The sputum is negative except for the presence of many streptococci. The urine is pale, cloudy, acid, specific gravity 1012. It contains no reducing substance. The addition of concentrated nitric acid causes a heavy, white, sticky precipitate which on boiling almost entirely disappears but reappears on cooling. The first 24 hour specimen of urine is 550 cc. in amount, pale, cloudy, acid, specific gravity 1015, Bence-Jones protein, 0.7 per cent (Esbach). The sediment shows occasional white blood cells and many squamous epithelial cells. On November 17 the elimination of phenolsulphonephthalein was zero in two hours.

November 12. Wassermann report by Dr. MacPherson. Inactivating serum at 60°C. for thirty minutes causes a heavy creamy precipitation. The clear filtrate gives a negative Wassermann reaction.

November 14. Roentgen report by Dr. Gladys Carr: Examination of the skull shows innumerable circular areas of rarefaction. The outlines are distinct; size varies from a diameter of about 1 cm. to one of about 1 mm. These areas are more numerous in the region of the anterior parietal bone. They are also seen in the mandible. In the shoulders there are similar findings in the proximal thirds of the humeri, in the acromion processes and in the distal ends of both clavicles. In the ribs are seen many old fractures through rarefied areas, especially marked in the left axillary region. There is a slight attempt at repair, with a moderate amount of new formed bone in the regions of the fractures. Bone atrophy is marked in all the ribs and in the entire spine. The intervertebral spaces are much narrowed. In the tibiae are a few small areas of rarefaction, and in the ilia, near the anterior aspects of both crests, the rarefied areas are rather large. In the proximal third of the femora may be seen similar abnormal findings. The findings are those of multiple myelomata.

Further blood examinations showed on November 16, hemoglobin

30 per cent (Sahli); red blood corpuscles 1,080,000; white blood corpuscles 8,800. Differential count: 250 cells, polymorphonuclears 76 per cent, myelocytes 4.8 per cent, lymphocytes 14.8 per cent, transitionals 2.4 per cent, large mononuclears 0.8 per cent, eosinophiles 0.8 per cent, basophiles 0.4 per cent, 5 megaloblasts, and many stippled red blood cells, anisocytosis and polychromatophila. On November 21 the blood showed a hemoglobin of 19 per cent (Sahli); red blood corpuscles 1,280,000; white blood corpuscles 6,200. Differential count: polymorphonuclears 81.2 per cent, myelocytes 7.6 per cent, lymphocytes 10.4 per cent, eosinophiles 0.4 per cent, basophiles 0.4 per cent. There were many normoblasts and megaloblasts seen in counting 250 cells and anisocytosis and poikylocytosis were pronounced.

A note made on November 21 is as follows: "For the last two days the patient has had to be catheterized. He has gone steadily down hill; his anaemia progressively has increased, and he has eaten but little. Whenever there has been evidence of pain he has been given morphine immediately. Last night his temperature rose to 102° and this morning it is 103°. In the evening he suddenly became pulseless and his respirations changed to a very markedly periodic character. He became unconscious and never regained consciousness. At this time the fronts of the lungs were negative save for a slightly harsh respiration over the right apex, but the character of the respiration was entirely masked by the numerous rhonchi. The patient died on November 21 at 9.07 p.m. from respiratory failure."

Autopsy was performed thirteen hours after death by Dr. E. W. Goodpasture.

Anatomical diagnosis. Multiple myelomata involving ribs, sternum, vertebra, skull, and femur; right broncho-pneumonia; acute fibrinopurulent pleuritis, right; chronic diffuse nephritis; fatty degeneration of the liver; adenoma of pancreas; hypertrophy of prostate; chronic adhesive peri-orchitis, left. (Of the autopsy description only the notes on the kidney and skeletal system need be given.)

Kidneys. Embedded in large amount of perirenal fat. Capsule is adherent. When the capsule is stripped off the kidneys are found to be very small and pale with surface made granular and irregular by innumerable cysts varying in size, most of them being about 1 to 2 mm., largest 1.5 cm. in diameter. Most of these cysts appear clear and yellowish, although others are opaque and whitish. On section the pallor of the kidney is very striking. Striation is completely obliterated. The left kidney weighs 75 grams. The right kidney is similar in appearance to the left kidney and about the same size.

Microscopic study of the kidney shows that the capsule contains a few small atrophic scars. Directly beneath it there are a few small cysts containing a serous fluid. The arteries show considerable thickening; the glomerular capillaries are markedly hyaline and thickened, many glomeruli being hyalinized. There is a diffuse connective tissue increase in the stroma of the cortex. Bowman's capsule is thickened everywhere. The cortex is atrophied and oedematous. There are a large number of hyaline casts present. The connective tissue increase and atrophy of the renal tissue is most marked in the pyramids.

Skeletal system. When the sternum is removed numerous enlargements along the course of most of the ribs can be seen, projecting more towards the thoracic cavity than outward. These enlargements are fusiform in shape and vary in color from reddish purple to pale gray. On palpation some of them are found to be covered by a thin shell-like layer of bone which breaks easily on pressure, causing crepitation. Others feel as if they are lined simply by a thick tissue membrane. On section these enlargements are found to be tumor masses rising from the medullary portion of the bones and growing outward, destroying the bony tissue with their advance. In several such areas fracture had occurred. On cut section the tumor masses vary in consistency from a softness like that of normal bone marrow to a great firmness. The color, structure and characteristics vary with consistency. The softer ones are largely reddish in color or they have a reddish purple center with a grayish semi-translucent zone about them. The hard areas are composed entirely of gray semi-translucent compact tissue which has a rather nodular appearance on cut surface. These tumors are found in many ribs and on one of the thoracic vertebrae extending inward. Section through the body of the sternum shows it to be filled with purple marrow-like material in which are small areas of gray, translucent, evidently tumorous tissue.

Sections of the tumor show it to be composed of medium sized polygonal cells lying in a loose reticular stroma. These cells are basic in reaction and have a definite outline. These nuclei are large, occupying one-half to one-third of the cell. They are reticular and clear, chromatin being arranged about the nuclear membrane. These nuclei are eccentrically placed, having about them an acidophilic crescentic zone. Cytoplasm about this zone is basophilic. There is an acidophilic nucleolus in each nucleus. The tumor is a myeloma of the plasma cell, non-granular, non-oxydase type.

This then was a typical case of multiple myeloma. Blood was taken in small amount; the patient's severe anaemia made it seem unwise to bleed more than a small amount. As much urine was collected as was possible during the brief period of the patient's stay at the Peter Bent Brigham Hospital. Study of the blood and urine yielded the following results.

QUALITATIVE METHODS

The protein obtained from the urine by precipitation at 54° was washed five times with distilled water and centrifugalized each time for ten minutes. A suspension in distilled water was used for the following observations: (1) A faint opalescence remained at 90° but most of the substance had dissolved, beginning to do so at about 80°. Cooling caused a definite increase in turbidity. (2) Suspension was treated with excess of glacial acetic acid. It partially cleared in the cold and totally at 70°. (3) Suspension was treated with one drop of concentrated HNO_3. A curd formed at 80° which partially dissolved on boiling for five minutes, with an increase of turbidity appearing on cooling.

The urine and isolated protein gave a strongly positive biuret reaction. Boston's (7) test for loosely combined sulphur was strongly positive on the protein. This test consists, briefly, in making the urine alkaline with strong NaOH solution, heating to boiling and then adding several drops of 10 per cent lead acetate solution and continuing the boiling. The creamy precipitate becomes brown, dark brown, and finally dull black when the test is positive.

The protein was precipitated completely from the urine on one-half saturation with ammonium sulphate. When it was dissolved in distilled water it gave the characteristic reactions. The protein dissolved in 10 per cent Na_2CO_3 solution did not pass through a dialysing membrane nor was it precipitated by dialysis.

The patient's urine when heated to 54°C. formed a dense white precipitate of rather sticky consistency. At 90° this was almost entirely redissolved although some cloudiness remained. Two drops of glacial acetic acid were added and the heating continued to boiling. The urine became clearer on boiling with acid than without the acid. On cooling under a stream of cold water a definite increase in turbidity was noted.

Acidulation of the urine with concentrated HNO_3 caused an abundant creamy precipitation in the cold. On boiling, the curds assumed a peptone-pink tinge and in a minute were practically entirely redissolved. Cooling caused a prompt return of the heavy deposit. The same phenomenon was observed upon the addition of concentrated HCl, which is Bradshaw's test for the Bence-Jones protein.

The addition of picric acid to the urine caused a heavy yellow precipitation in the cold. This was washed repeatedly with distilled water to remove excess of picric acid. The substance thus precipitated dissolved completely on boiling with distilled water and reappeared on cooling. A slight excess of glacial acetic acid was added to a suspension of the picric acid precipitate in distilled water and at 80° solution was complete, with no return on cooling. The addition to another portion of the same suspension of concentrated HNO_3 caused a prompt return of the substance out of solution. This precipitate after the addition of HNO_3 dissolved at 90° but did not reappear with the temperature lowered to 30°. Neutralizing this solution with NH_4OH produced no apparent change.

In doing the routine Wassermann test inactivating the blood serum at 56°C. for thirty minutes produced a heavy creamy precipitate. This precipitate was filtered off. The filtrate gave a negative Wassermann reaction. The precipitate was washed several times with distilled water to remove any traces of serum albumin and globulin. It was soluble in 10 per cent Na_2CO_3, gave positive biuret and Boston tests, and would not pass through a dialyzing membrane.

The washed protein substance from the blood and the washed material from the urine behaved in the same manner with the various chemical reagents used. A solution of the blood protein in 10 per cent Na_2CO_3 was added to normal urine. The addition of a few drops of concentrated HNO_3 produced a copious creamy precipitate which disappeared completely on boiling and reappeared on cooling. Acidulation of the urine with glacial acetic acid produced a slight white precipitate which became abundant at 60°C., almost entirely dissolved at 100°C., and reappeared on cooling.

These reactions indicate that the urinary protein and the abnormal blood protein are the same substance, each giving the characteristic tests for the Bence-Jones protein. The slight differences in reaction between the washed protein and the same substance in the patient's urine are probably due to the electrolytes present in the urine. This accords in a general way with the very complete studies of Hopkins and Savory (8). These writers found that for the typical phenomena of reversible heat changes to be complete, definite concentrations of salts are necessary.

QUANTITATIVE METHODS

To estimate the quantity of Bence-Jones protein in the blood serum it was first necessary to eliminate the large amount of serum albumin and globulin. A modification of the method of Folin and Denis (9) for the estimation of the urinary protein was used. The fluid portion of the clotted heart's blood was filtered and centrifugalized until clear.

Five cubic centimeters of serum in a weighed centrifuge tube was heated on a water bath at 58°C. for fifteen minutes. A heavy creamy precipitate formed. Fifteen cubic centimeters of 0.9 per cent NaCl was added and the tube whirled in the centrifuge for fifteen minutes. The clear supernatant fluid was poured off and gave typical reactions for serum albumin but negative reactions for Bence-Jones protein. The tube was then filled with cold distilled water and centrifugalized for fifteen minutes. This process was repeated several times to make sure that all serum albumin and globulin had been removed. The material was then washed repeatedly with 50 per cent ethyl alcohol. After drying over steam for five hours it was extracted with ether for four days to remove fats. It was then placed in a desiccator until a constant weight was reached. By this method the blood serum obtained from the heart at autopsy was found to contain 7.86 per cent of the Bence-Jones protein.

The quantitative method used for the determination of the urinary protein was the ordinary Esbach procedure and eight days and two days respectively before death the urine contained 0.7 per cent and 0.8 per cent. The filtrate from the urine, obtained after removal of the coagulum at 54°, showed no trace of albumin so it is doubtful if there was any present.

A feature of most of the cases of multiple myelomata reported has been the apparent selective action of the renal epithelium in permitting the excretion of a large amount of abnormal protein with a holding back of serum albumin. This has been the rule in cases with normal kidneys and frequently occurred in those which at autopsy showed interstitial or parenchymatous changes. In the present case where there was more severe renal damage as shown by the anatomical condition of the kidney at autopsy and by the defective 'phthalein excretion before death, no serum albumin was demonstrable in the urine while the foreign protein was excreted at the rate of 0.7 per cent to 0.8 per cent daily. However, apparently owing to the marked renal disturbance the Bence-Jones protein was literally "dammed back" in the blood stream where at the time of death it reached a concentration of nearly 8 per cent.

Other observers have noted evidences of renal disturbance in patients with myelomata and have examined the blood for Bence-Jones protein largely with negative results. The literature, however, on these two phases of the condition so strikingly shown in our case, is very meagre. Thomas (10) reported a case of multiple myelomata in which the urine contained 0.73 per cent of albumin and 0.225 per cent "albumose," and the sediment showed many hyaline and granular casts. There was no autopsy report. Parkes Weber (11) examined the heart blood from his case and was unable to obtain the slightest trace of Bence-Jones protein. However, he attributed his negative findings to the fact that only a limited quantity of blood was procurable for examination.

Polyuria and polydypsia with cylindruria and transitory albuminuria occurred in a case reported by Collins (12). Autopsy showed chronic interstitial nephritis. Coriat (13) found Bence-Jones protein present in the pleuritic fluid of a case of alcoholic polyneuritis in a concentration of 4 per cent with negative findings in the urine. The patient died some time later and autopsy showed miliary tuberculosis but no bone lesions (14).

The only other instance reported where there was demonstrable Bence-Jones proteinemia is the case of Ellinger (15). He found in the blood and ascitic fluid of a case of multiple myeloma a substance which gave the typical reactions of the Bence-Jones body but it was not present in measurable amount. The kidneys were of normal size and showed only slight fatty changes.

The case of Hopkins and Savory (8) at autopsy showed definite interstitial nephritis. Folin and Denis (9) have noted the frequent occurrence of a few hyaline and granular casts in cases of myeloma with no clinical evidence of nephritis. Groat and Brewer (16) recently reported a case which had a 'phthalein output of 20 per cent, blood pressure of 130 to 135 systolic, and a high blood nitrogen.

The theories as to the origin of the protein are nearly as numerous as the number of cases reported. Bence-Jones thought it to be an "albumose." Magnus Levy, who has obtained it in crystalline form, showed it is closely related to true albumin. The fact that it yields albumose on digestion and metaproteins on treatment with acids and alkalies indicates that it is higher in the scale of protein decomposition products than the proteoses.

Huppert believes it to be a heteroalbumose; Kuhne and Chittenden, that it is closely related to the globulins. Simon thinks that it is probably derived from the blood albumins through the action of enzymes from the abnormal plasma cells of the bone marrow. In the present case this seems to be the most logical explanation of the origin of the substance.

In Coriat's case of polyneuritis the protein was present in large amount in the pleuritic fluid while none was found in the urine. He explained it as possibly due to the action of a pathological pleuritic fluid on the exuding native blood proteins.

According to Austin (17) the prolonged action of bacteria on fibrin and nucleins and possibly other proteins produces proto and heteroalbumoses. This might serve to explain the formation of Bence-Jones protein in Coriat's case as autopsy showed miliary tuberculosis and no evidence of bone involvement.

DeCastello regarded the protein as a product of diseased renal epithelium, and claimed that it was never demonstrated in the urine when the kidneys were normal. However, many cases which have come to autopsy have shown practically normal kidneys when during life there had been a heavy daily output of the protein. In the present case with much damaged kidney tissue there was an output of 0.8 per cent with retention of a much larger amount.

That it is a foreign protein in the tissues is the opinion of Abderhalden; and Ellinger, Stokvis, and Matthes by injecting it into dogs intravenously and per rectum found that it was excreted unchanged. The theory of Magnus Levy that it is a product of abnormal exogenous protein metabolism has been rendered improbable by the work of Folin and Denis (9), and Hopkins and Savory (8), and Groat and Brewer (16), who found that the output of the protein was not influenced by changes in diet.

Abderhalden and Rostoski (18) by several injections into rabbits produced precipitins which reacted alike with the Bence-Jones protein and human serum and its proteins. The same observation was made by Boggs and Guthrie (19). Antihuman serum will react with the Bence-Jones protein, according to Hopkins and Savory. That the substance is very closely related to the blood albumins is indicated by these researches.

Fleischer found a substance giving similar reactions to Bence-Jones protein in normal marrow but this has never been confirmed. Wood and Parkes Weber have obtained it from tumor tissue and Ellinger from tumor, ascitic fluid and the blood.

The bulk of opinion at present is that it is of endogenous origin, probably derived from the blood proteins through the action of the abnormal cells of the bone tumor, and having properties which place it nearer the true albumins than the proteoses.

SUMMARY

1. The case reported is one of multiple myelomata of the plasma cell, non-granular, non-oxydase type.

2. This is the first instance reported where there was associated definite clinical evidence of advanced nephritis with retention of a large, measurable amount of the Bence-Jones protein in the circulating blood.

The writer wishes to express his deep appreciation to Dr. Henry A. Christian for the privilege of reporting this case and for his kind advice and criticism. Also he wishes to thank Dr. E. W. Goodpasture for many valuable suggestions.

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INJURIES TO THE PANCREAS FOLLOWING OPERATIONS ON THE RIGHT KIDNEY

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Many varied complications following operations on the kidneys have been recognized and reported during the past twenty-five years, which have witnessed the development and perfection of the technique of renal surgery. However, no references have been found, in the extensive literature on the subject, to the grave, though fortunately rare, complication which may arise as a result of accidental injury to the pancreas during the course of operative procedures upon the kidney. Two kidney cases recently operated upon, in which definite evidences of pancreatic injury could be demonstrated, would seem to justify a consideration of the condition under which such an injury would be likely to occur and how it can best be avoided.

It seems highly probable that in a not inconsiderable number of cases complicated with extreme abdominal distension following an operation on the kidney, the causative factor is an unrecognized injury to the pancreas. So-called post-operative adynamic ileus is a condition familiar to all surgeons doing kidney work and while a fatal result due to this cause is a rarity, owing to the present high standards of operative technique and post-operative treatment, yet a certain number of these cases do occur and we believe that a certain proportion of them can be explained as a result of accidental damage to the pancreas unrecognized at the time of operation.

From a consideration of the anatomical relations of the pancreas with the kidneys it would first appear that the former organ would be more liable to accidental damage during operative procedures on the left kidney since the tail of the pancreas is in direct contact with that kidney. Piersol (1) states that the head of the pancreas lies between the first and third parts of the duodenum close against the second part. "It rests behind on the inferior vena cava, sometimes on the right renal vein and may approach the right suprarenal body." The posterior surface of the tail lies on the vena cava, aorta, the left pillar of the diaphragm, the left suprarenal capsule and the left kidney. These relations are well shown in figure 3.

Piersol further states that "the pancreas . . . . is entirely retroperitoneal. The posterior surface, with the possible exception of the end of the tail, which may be surrounded by peritoneum, is attached to the parts behind it by connective tissue." Although the tail of the pancreas is in direct contact with the left kidney it is less liable to accidental injury on account of its mobility and lack of firm attachment and is easily pushed aside during an operative procedure. The head of the pancreas, however, is firmly attached to the flexure of the duodenum and to the structures which lie behind it so that it is relatively immobile and might be exposed to injury when the duodenum is retracted upward towards the median line in exposing the right kidney.

It can also readily be understood how an injury to the head of the gland would be a far more serious affair than a similar injury to the tail. The former is larger and relatively more vascular and the extravasation of pancreatic secretion about the important structures with which the head is in relation would certainly provoke more serious consequences than a similar occurrence in the tail which is more or less remote from the larger vessels and sympathetic ganglia. By a study of figure 3, in which the relations of the pancreas with the kidneys are shown in cross section, the possibility of injury to the pancreas during attempts to control a hemorrhage arising in the region of the vena cava will be easily understood. The relative immobility of the head of the pancreas in comparison with the tail is also here shown, and can be understood better when one remembers that the flexure of the duodenum is retroperitoneal and more or less fixed.

A few cases have been observed in this clinic in which extreme abdominal distension followed kidney operations. In one of them it was found necessary to perform an enterostomy for the relief of the obstruction, following which the patient made an uninterrupted recovery. The remaining cases of uncomplicated distension yielded rapidly to the usual simple methods. The two cases in which the pancreas had suffered injury are given in detail on account of their rarity and interest.

Case 1. Renal calculus. Right nephrotomy. Bleeding from aberrant vessel, stopped by blind clamping and pressure. Post-operative intestinal obstruction. Enterostomy. Death. Autopsy: Pancreatitis, fat necrosis.

J. F. W., aged 42 years. Admitted to the urological service October 30, 1913, complaining of frequency, urgency and burning on urination.

The family history and past history are unimportant.

The present illness began about two years previously with an attack of slight hesitation and difficulty of urination, later followed by frequency and urgency and slight incontinence accompanied by burning. This attack passed off in a few days but similar attacks recurred at intervals until the patient was forced to seek medical advice for their relief. At no time has he noticed blood in the urine and has never suffered from pain in the back or radiating pains suggesting renal colic.

The physical examination revealed a strongly-built, rather obese man. No abnormalities were discovered, the kidneys were not palpable and there was no tenderness in the kidney region.

The urine was cloudy, containing a heavy precipitate of albumin, pus cells and bacilli, but no red blood cells. An X-ray examination showed some indefinite shadows in the region of the right kidney. A cystoscopic examination showed no enlargement of the prostatic lobes. The bladder mucosa, aside from slight trabeculation, was essentially normal. The right ureteral orifice was more prominent than the left but otherwise normal in appearance. Both ureters were easily catheterized, the urine from the right kidney containing numerous pus cells and bacilli and excreting 15 per cent phenolsulphonephthalein in one-half hour. The urine from the left kidney was normal and excreted 25 per cent phenolsulphonephthalein in one-half hour.

A pyelogram of the right kidney showed a mild grade of hydronephrosis with blunted calyces and dilated ureter.

On account of the relatively slight diminution of the function of the right kidney it was decided best to remove the stones by a pyelotomy or nephrotomy and on October 31, under gas and ether anesthesia, the kidney was exposed by Dr. Young, a large incision being necessary. The kidney was found quite adherent at the upper pole and during the division of these adhesions a clamp slipped and immediately an active hemorrhage occurred which was recognized as arterial. The vessel retracted into the depths of the wound but the hemorrhage was soon controlled by clamps which had to be applied rapidly in the deepest part of the wound and by firm pressure by means of packs. The operation then proceeded uneventfully, one stone being removed through a small incision in the pelvis and three others from the lower calyx through a nephrotomy incision done in the usual way with a silver wire, bleeding being controlled by a rubber tube around the vessels. There was no further hemorrhage and the wound was closed in the usual way with drainage. The patient left the table in excellent condition and was apparently little if at all shocked by the active hemorrhage during the first part of the operation.

The post-operative course was normal for the first twenty-four hours, when the patient became more restless with faster pulse. Soon after, considerable abdominal distension was noticed with partial anuria and the patient became restless and toxic in appearance. Ths distension increased rapidly and all efforts to move the bowels were ineffectual. The patient started to vomit forty-eight hours after operation; and twelve hours later, the symptoms having progressed rapidly, the abdomen was opened through a right rectus incision. Extreme distension of both small and large intestine was noted but no obstruction was found and no fat necroses seen. A rapid enterostomy was done, a large amount of gas escaped and there was fair relief of the distension. This relief, however, was only temporary as the extreme distension rapidly reappeared, soon followed by fecal vomiting, and the patient's condition became gradually worse until he died four days after the first operation.

Necropsy. Anatomical diagnosis: Right nephrotomy operation; intestinal obstruction; acute pancreatitis; diffuse fat necrosis; portal thrombo-phlebitis; pseudo infarct in liver; thrombosis of branch of right renal artery; necrosis of the upper pole of right kidney and healing surgical wound; congestion and broncho-pneumonia of lung; distension of intestine; wound of recent colostomy operation; focal necroses of liver.

"When the peritoneal cavity is opened the small bowel protrudes from the opening and is greatly distended with gas and fluid. The distension is uniform throughout the intestinal tract. There is a slight excess of fluid in the peritoneal cavity and a few fibrinous clots are found in the pelvis. There is a localized fresh inflammation around the recent surgical wound. The colon is drawn up to the abdominal wall and fixed, forming a colostomy. Near the site of the wound and the lower portion of the ileum a loop of bowel is bound together by fresh, fibrinous adhesions due apparently to trauma at operation. The peritoneal surfaces are smooth and shiny elsewhere. Beneath the peritoneum on the right side extending down into the pelvis and up the left side of the pelvis is a deep blue extravasation of blood. At the base of the mesentery leading up to the first portion of the colon are found numerous yellow opaque dots measuring about 3 or 5 mm. in diameter, which are just beneath the peritoneum and are occasionally surrounded by injected blood vessels. These opaque dots, which are apparently fat necroses, are more numerous as the region of the pancreas is approached. Also in proportion to their frequency are seen the extravasations of blood conforming to the region of the recent nephrotomy operation. The head of the pancreas lying in the curve of the duodenum is superficially necrosed. The connective tissue and fat lying over the pancreatic tissue is of a dirty greenish color and has undergone softening. There are numerous fat necroses surrounding the head of the pancreas and scattered through the base of the mesentery. Some of these have undergone softening.

"The lower pole of the right kidney, upon which the nephrotomy had been performed, lies just adjacent to the head of the pancreas in this area and the trauma resulting from operative maneuvers at this point seems to have been responsible for the stretching, bruising and injury to the tissues. Through the substance of the pancreas there are numerous focal necroses but no hemorrhages. The pancreatic tissue is rather firm. At the base of the mesentery is the seat of the most widespread and destructive fat necrosis, and on the right side in the fat of the ascending colon.

"The liver shows numerous minute focal necroses, a pseudo infarct of the right lobe and the portion of the portal vein, just opposite the pancreas, is the seat of a thrombo-phlebitis.

"The left kidney is normal in appearance.

"The right kidney is surrounded by considerable extravasated blood and fibrinous exudate. The tissues beneath the peritoneum surrounding the kidney and descending to the pelvis contains considerable extravasated blood. The entire surface of the kidney is covered by fibrinous adhesions. The incisions into the kidney substance are beginning to heal. There is a slight amount of pus about the sutures and considerable granulation tissue over the lower pole, which is very friable and hemorrhagic. The upper pole is very soft, flabby and necrotic in a zone immediately around the pole. This soft dead tissue is separated from the normal kidney substance by a light zone somewhat elevated from the surrounding tissue. On dissecting out the renal vessels on this side the main stem comes off normally from the aorta. At a point about 1 cm. from its origin, it sends off a large branch which in turn sends off a branch to the adrenal and which is thrombosed from a point just above the origin of its adrenal branch. Although this vessel cannot be traced in the kidney substance it seems to be quite evidently a vessel supplying the upper pole of the kidney, the thrombosis of which has caused the necrosis. There is a great deal of inflammation throughout the kidney, the result of the operation, but the majority of the kidney substance is otherwise normal. The pelvis of the kidney is slightly dilated and inflamed. Its mucous membrane is hemorrhagic, and extending down into the lower pole it is very granular, thickened and injected.

"The bladder is normal. The prostate contains numerous pinhead sized calculi but is otherwise normal. The seminal vesicles and teste are normal.

"The intestines are greatly dilated, the mucous membrane pale and slightly oedematous with a few petechial hemorrhages.

"The aorta is elastic and has a smooth internal surface.

"The heart is normal and the myocardium shows no changes on section.

"The lungs show a marked bronchitis with areas of bronchopneumonia and a few small healed tubercles. The spleen is normal."

Microscopic notes. "The sections from the right kidney show an infected infarct with beginning organization. Much hemorrhage is seen in other areas.

"Sections from the pancreas show a few necrotic cells about the margin with extensive peripancreatic fat necrosis."

Comment. The active hemorrhage which occurred during the exposure of the kidney was almost certainly due to the aberrant artery which was demonstrated at autopsy and which supplied the necrosed portion of the upper pole of the right kidney. Attempts to control this branch after it had retracted into the depths of the wound resulted in injury of the head of the pancreas either by forcible packing or what is more probable, the application of clamps to the pancreatic tissue itself, resulting inevitably in necrosis and extravasation of pancreatic secretion.

Case 2. Right renal calculus. Operation; kidney very adherent at upper pole; pyelotomy. Post-operative intestinal obstruction, requiring enterostomy. Development of glycosuria. ℞: *Pancreatine. Slow convalescence and cure.*

F. W., aged 42 years. Admitted to the service of Dr. J. T. Geraghty, October 28, 1912, complaining of cloudy urine and frequent urination.

The family history is unimportant.

The past history is unimportant except for a light attack of typhoid fever at the age of 35 and a "nervous breakdown" five years later which yielded rapidly to rest treatment.

The present illness began four years ago with frequence of urination and some burning. Soon after the patient noticed that the urine was cloudy and it has never cleared up since this time. There was also a dull, aching pain across the right side of the back which was made worse on exertion. He has had at no time radiating pains or symptoms of kidney colic and has never noticed any blood in his urine.

The physical examination revealed no abnormalities except slight tenderness in the right costovertebral angle on deep pressure. The urine contained a trace of albumin and large number of pus cells with a few red blood cells.

An X-ray examination revealed a definite shadow in the region of the kidney. The ureters were not catheterized.

On October 29, under ether anesthesia, the right kidney was exposed by Dr. Geraghty and delivered into the wound after considerable difficulty due to firm adhesions at the upper pole. These were divided between clamps and no unusual hemorrhage was encountered. The stone was removed through a small incision in the pelvis and the wound closed in the usual manner with drainage. The patient left the table in good condition and suffered no shock from the operation.

On the following day the abdomen became markedly distended and the usual measures to move the bowels were ineffectual. The pulse became rapid and poor in quality. With the gradually increasing distension, the patient's condition became progressively worse with persistent nausea and vomiting which could not be controlled by gastric lavage.

On October 31 the abdomen was opened and enormous distension of the whole intestinal tract found without any apparent cause. No fat necroses were noticed. An enterostomy was done rapidly and it was thought that the distended loop chosen was rather high in the intestinal tract.

The patient's condition remained critical for several days but with the gradual relief of the distension there was slow improvement. The enterostomy tube was removed four days after the operation and liquid diet was instituted. Although there was little discharge from the enterostomy and the patient was taking nourishment fairly well with more or less regular bowel movements, his condition slowly became worse with subnormal temperature, rapid weak pulse and the general picture of inanition in spite of all supporting treatment. The stools contained large amounts of fat droplets and undigested muscle fibres. A bed sore had also developed and was slowly increasing. On December 3 sugar was present in the urine but tests for acetone and diacetic acid were negative. On December 8, pancreatin, gr. xv and calcium lactate gr. xv, three times a day, were started and the patient given a modified soft diet. There was a rapid and surprising improvement in the general condition and the sugar disappeared from the urine on December 13 and was never present at subsequent examinations, and the fat and muscle fibres disappeared from the stools. During this time the enterostomy wound was still open and discharging small amounts of intestinal contents. The patient now began to gain strength rapidly and the enterostomy was closed on January 7. The kidney incision had already healed except for a small sinus, and the bed sore was granulating nicely.

The patient was discharged on February 24, still taking pancreatin. Several weeks later this was discontinued and he progressively regained his strength.

Comment. No lesion of the pancreas was demonstrated when the abdomen was opened in this case and it is difficult to conceive of an injury sufficiently extensive to interfere with the secretion of the gland without causing the death of the patient from pancreatitis and its sequelae. The inanition was almost certainly not due to the simple starvation caused by a high enterostomy, since the latter was discharging only small amounts of intestinal contents and the patient began to have normal bowel movements as soon as the extreme distension had been relieved. The remarkable improvement following immediately on the administration of pancreatin and the coincident rapid disappearance of sugar from the urine were most suggestive of definite interference with the normal functioning of the pancreas and with the clinical picture of the rapid onset of extreme distension without other demonstrable cause, lead to the assumption that the pancreas had received some injury, most probably while the kidney was being freed during the earlier stages of the operation. The extent and nature of the lesion remain obscure but it is certain that there was no extensive extravasation of secretion into the tissue about the pancreas, as experience has shown that such an accident, from whatever cause, is almost invariably and rapidly fatal.

The following case is another example of the severe distension leading to intestinal obstruction which is not infrequently seen after right sided renal operation. However, in this case there was no demonstrable injury to the pancreas either at the time of the enterostomy operation or in the subsequent post-operative course.

Case 3. Nephrectomy for large hypernephroma. Difficult operation on account of hemorrhage. Post-operative nausea, vomiting and distension. Intestinal obstruction requiring enterostomy on fifth day. Recovery.

A. E. A., aged 66 years. Male, admitted December 15, 1912, complaining of hematuria of seven months' duration. Two months ago was subjected to prostatectomy (elsewhere). Hematuria continued.

Examination showed large tumor of right kidney.

Operation. Young, December 16, 1912. Right nephrectomy, extraperitoneal. Very difficult on account of vascularity and deep hemorrhage. Very forcible traction toward median line necessary in exposure of kidney pedicle. Vessels ligated. Wound drained and closed partially.

On day following operation patient had nausea and distension which increased steadily despite all measures undertaken. On fifth day (December 21) intestinal obstruction was so marked that laparotomy was performed through right rectus. In the right flank a large, tightly distended loop of intestine was palpated, and as it was impossible to bring this over toward the wound a second (gridiron) incision was made, just above McBurney's point over the distended loop which was sutured to the opening. The intestine was then opened, one quart of brownish fecal fluid evacuated through tube. Impossible to say whether distended gut was large or small intestine.

Convalescence. Considerable shock, nausea and vomiting. Bowel irrigated q. 4 h. Slow recovery. Stool on fourth day.

December 31. Closure of enterostomy under cocaine. Gradual convalescence. Closure of all wounds.

February 14, 1913. Discharged in good condition.

Comment. The occurrences in this case were similar to but not so grave as those in Case 1. It seems probable that in isolating the pedicle, freeing the tumor, clamping bleeding vessels and forcible traction against the peritoneal contents, traumatism was probably done to both the pancreas and adjacent intestine, and that intestinal distension, obstruction, etc., were thus produced. Care in hemostasis, avoidance of blind clamping, and to forceful deep retraction, are precautions which should evidently be taken.

Mayo (2) has observed three cases of injury to the duodenum as a result of operations on the right kidney, all of which were eventually fatal. He states that the duodenum can be injured only if there is considerable infiltration about the pedicle and emphasizes the fact that the flexure of the duodenum is retroperitoneal and more or less fixed. In previous communications the same author (3) (4) has emphasized the importance of a good exposure of the kidney to avoid accidents during the course of the operation and especially recommends mobilization of the twelfth rib by division of the costo-vertebral ligaments.

Severe hemorrhage during the course of an operative procedure upon the kidney usually occurs during the separation of adhesions about the upper pole, when an aberrant vessel is liable to be injured, or may take place from a shortened, infiltrated pedicle. In the management of such a pedicle Gerster (5) advises that the veins be clamped and ligated first and states that if the artery is tied before the veins, the latter may tear off when the pedicle is unduly infiltrated and retract into the deeper portion of the wound. In seeking to combat such a hemorrhage it can easily be understood how serious injury might be done to the duodenum or pancreas by the application of clamps or by too vigorous packing.

In freeing the upper pole in order to deliver the kidney into the wound great pains must be taken to avoid tearing any adhesions and any which are present should be carefully divided between clamps and immediately tied to avoid the danger of the clamp pulling off or cutting through the adhesion during the remainder of the operation. This precaution is especially important on account of the frequency of anomalous distribution of the renal blood supply. Gray (6) states that "frequently there is a second renal artery which is given off from the aorta above or before the renal artery proper, the former being the more common position. Instead of entering the kidney at the hilum the accessory renal artery often pierces the upper or lower pole of the gland." Rupert, (7) in a study of the vascularization of the kidney in a series of cadavers, found anomalous distribution in 70 per cent. Aberrant vessels to the upper pole were found to be of a more frequent occurrence than similar vessels to the lower pole. Dorland (8) concluded that irregularities in the blood supply, which he observed in various types of renal anomalies, could be explained by the incomplete ascent of the kidney, which condition is usually present in such cases. Papin and Iglesias (9) state that aberrant vessels occur in almost all cases of renal anomalies and in general found greater irregularity in the distribution of the arteries than in that of the veins.

The embryology of the renal blood supply has been studied by Pohlmann (10), Hill (11), Castellani (12), and others. These observers found that the kidney does not receive its blood supply until it has finally reached the situation in the body which it should occupy in the adult, and any factors tending to interfere with the normal ascent of the gland will predispose to anomalous vascularity.

The early recognition of injury to the pancreas following an operation upon the kidney is extremely difficult or quite impossible and unless the probability of such an occurrence had been noted during the course of the operation, the condition would probably only be recognized at a later operation or at autopsy. The progressive and extreme distension with its attendant persistent vomiting and abdominal pain and the rapid prostration of the patient are signs of a serious intra-abdominal catastrophe, and in the three cases observed the evident intestinal obstruction made a laparotomy and enterostomy imperative. In his studies of acute pancreatitis, Körte (13), (14) advises incision and drainage of the involved areas of the gland but in cases following a kidney operation the condition of the patient is usually so grave as to forbid any other procedure than a rapid enterostomy for the relief of the obstruction. If, however, the patient's condition permits an exploration of the region of the pancreas such examination should be carried out and any necrotic portions removed. Drainage should be instituted, but it is felt that the incision of non-necrotic areas is still a mooted question.

The preparation of a patient before a kidney operation should be most careful and especial attention should be placed on the thorough evacuation of the intestines in order to avoid the so-called paralytic ileus which may lead to extreme distension and render enterostomy necessary. It has been the practice in this clinic to administer castor oil the evening before the operation is to be performed and an enema is given before the patient is taken to the operating room. A routine hypodermic injection of morphine gr. $\frac{1}{4}$ and eserin gr. $\frac{1}{60}$ is then given, as we believe that by the action of the latter drug troublesome post-operative distension is less liable to occur.

CONCLUSIONS

1. Injury to the pancreas during operations on the right kidney may occur and it seems probable that some cases of extreme abdominal distension following such operations are due to unrecognized injury to the pancreas resulting in acute pancreatitis.

2. Such injuries can be best avoided by an adequate incision for the exposure of the kidney and careful ligation of all structures divided in freeing the upper pole; and the probability of the presence of anomalous vessels must be kept in mind and care taken to ligate them securely.

3. Injury to the pancreas should be suspected following operation on the right kidney in the presence of extreme abdominal distension and rapid prostration.

4. Rapid enterostomy offers a chance of preserving life by relief of the intestinal obstruction but if the injury is extensive

enough to cause widespread extravasation of pancreatic secretion the condition is hopeless.

5. Traumatism to intestine by retractors, clamps or gauze packs may also cause intestinal distension or even obstruction.

6. Care in hemostasis and good exposure without violent retraction and traumatism is of prime importance in renal surgery.

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PLATE 1

Fig. 1. Abdominal Viscera from Behind, Kidneys Removed, Showing Areas of Contact with Other Organs

From Kelly and Burnam

INJURIES TO THE PANCREAS
H. H. YOUNG AND J. A. C. COLSTON

PLATE 1

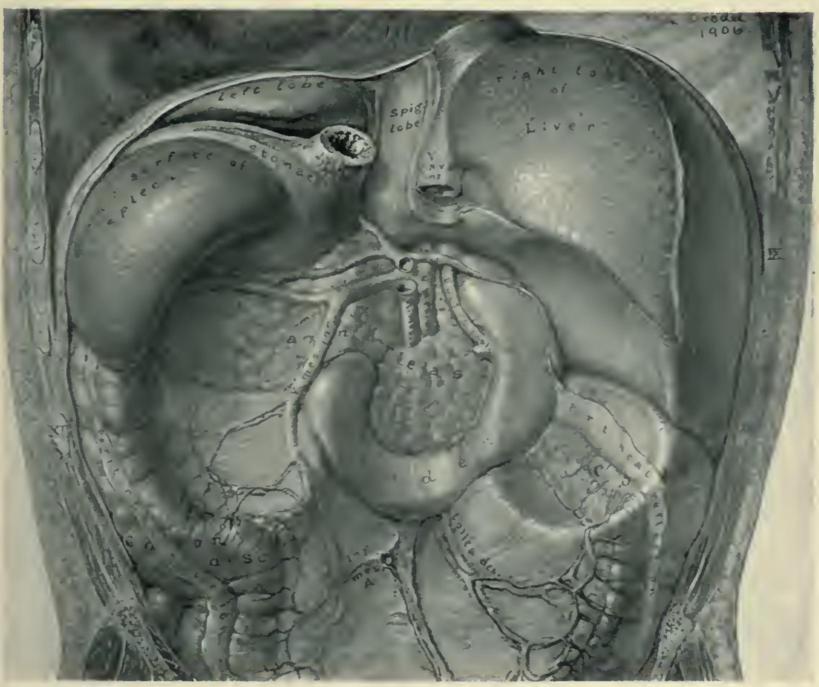


PLATE 2

Fig. 2. Drawing of operation (Case 1) at which an aberrant artery to the upper pole of the kidney was found. The clamps and packing shown were introduced to stop the hemorrhage.

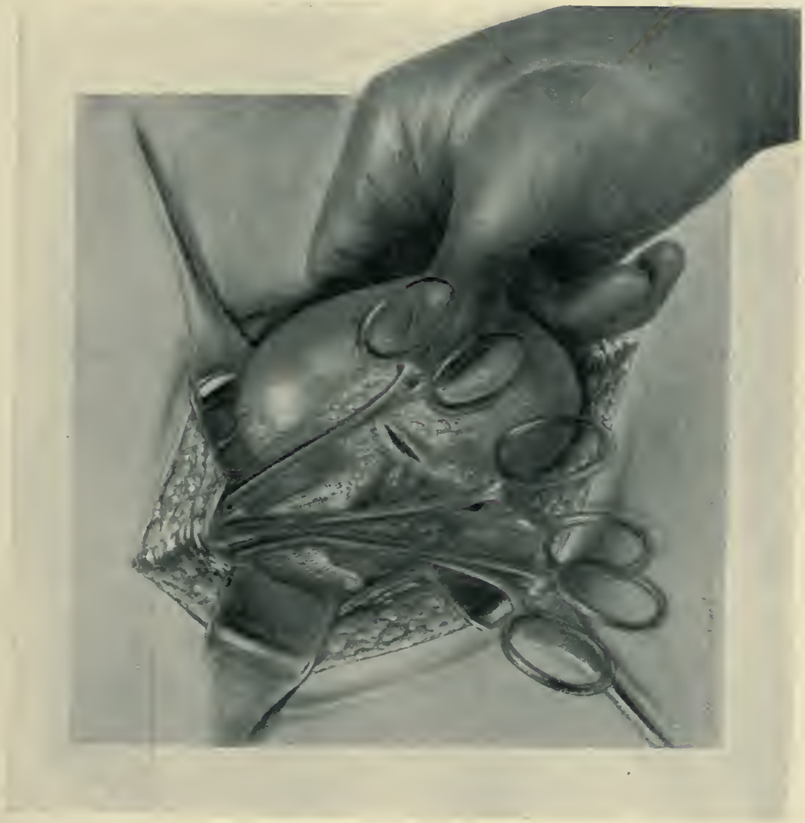


PLATE 3

Fig. 3. Cross-section of cadaver at level of first lumbar vertebra. The nearness of the right kidney to the pancreas and duodenum is shown. The peritoneum extends around the duodenum about as far as the point of the gall bladder as drawn. The fixation of the head of the pancreas and its proximity to the large vessels and kidney are evident. The tail although in contact with the left kidney is more mobile.

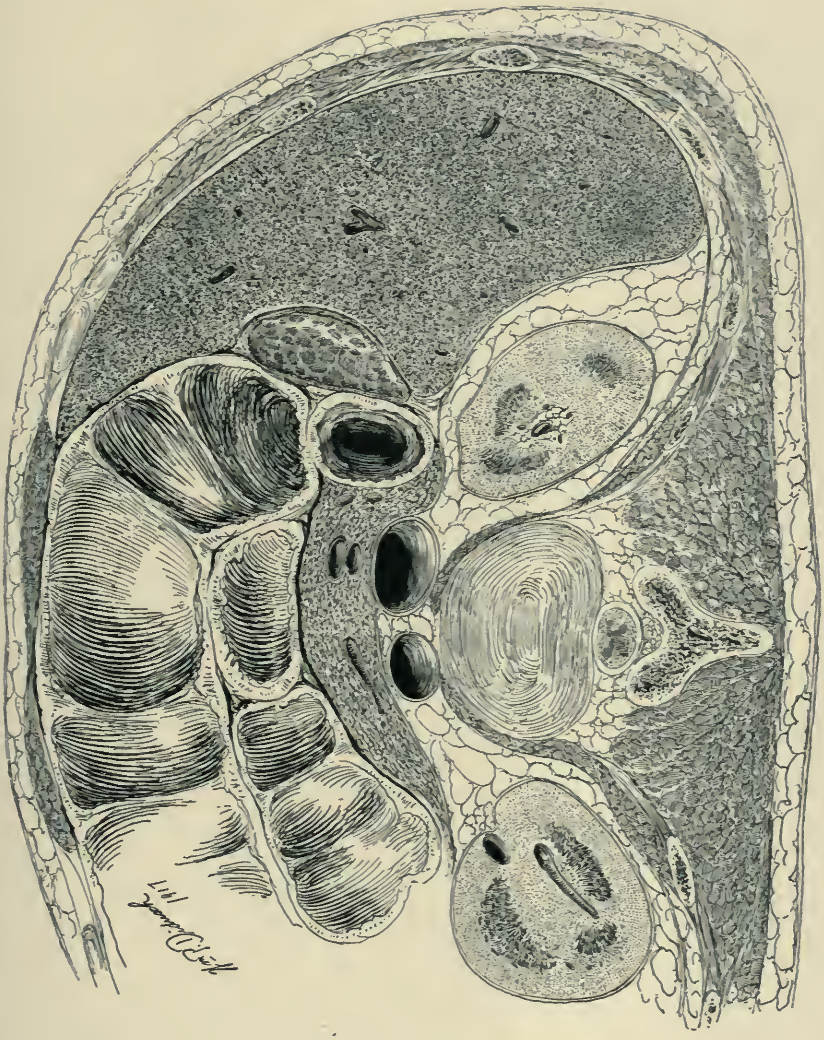
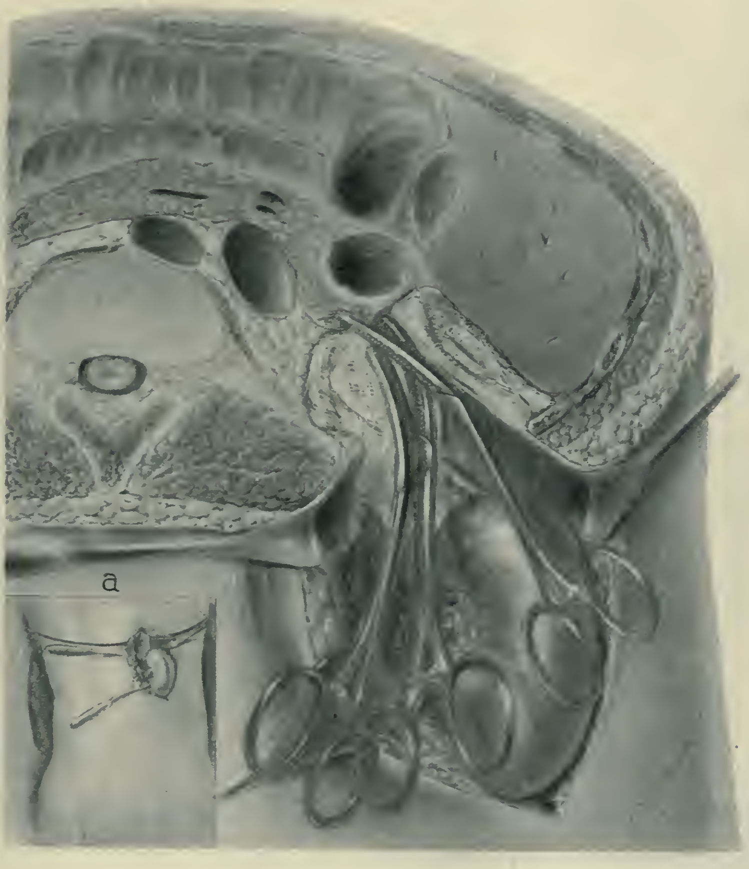


PLATE 4

Fig. 4. Schematic representation of the manner in which clamps and packing introduced through the kidney incision in an effort to arrest sudden hemorrhage reached the pancreas. One sees the close relationship between the head of the pancreas and the duodenum which is retroperitoneal and firmly fixed. The aberrant artery to the upper pole of the kidney, the cause of the hemorrhage, is shown. *A* represents the patient's body as it rests on the kidney pad at operation, and serves to orient the larger picture. The line represents the level at which the section is drawn.

PLATE 4



ON THE COMPARATIVE INFLUENCE OF MORPHIN AND TOTAL OPIUM ALKALOIDS ON RENAL COLIC

DAVID I. MACHT

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The pains of renal colic are among the most excruticating met with in medical practice. We are all familiar with the graphic description by Montaigne, who was a sufferer for many years, which is quoted by Osler:

> Thou art seen to sweat with pain, to look pale and red, to tremble, to vomit well-nigh to blood, to suffer strange contortions and convulsions, by starts to let tears drop from thine eyes, to urine thick, black, and frightful water, or to have it suppressed by some sharp and craggy stone, that cruelly pricks and tears thee. (1).

For the relief of this horrible suffering injections of morphin are generally recommended. Unfortunately it is the experience of most clinicians that in this condition ordinary small doses of that drug are but of little use, and they must either be repeated or larger doses administered. Even large doses of morphine are sometimes of little avail and chloroform inhalations have to be resorted to.

In connection with a study of the pharmacology of the ureters or the action of various drugs on those organs, the results of which have in part already been published (2 and 3), the author has been investigating the behavior of the opium alkaloids individually and in combination with each other (4). The conclusions drawn from these experiments are of such practical interest, that it is deemed worth while publishing a note on the subject in this place.

METHOD

A simple and convenient method of studying the action of drugs on the ureters has been described in detail by the author elsewhere (2 and 3). Briefly, it consists in the use of rings of the ureters of pigs, and other animals. When a ring of the ureter of a pig or other animal is suspended in a proper medium (urea-Locke solution), under suitable conditions of temperature, oxygenation, etc., it begins to undergo spontaneous contractions, and will inscribe on a kymograph a curve not unlike that made by a preparation of the heart of a frog. In this way, by the introduction of drugs into the surrounding fluid, their effect on both the contractions or peristaltic movements and the tonus of the ureter may be observed. Having determined the action of a given drug on the ureter in this way, observations are made on the intact ureter in a laparotomized animal, to ascertain whether the same effect is produced in the intact animal as *in vitro*. Finally, whenever possible, experiments with rings of a human ureter from a case of nephrectomy may be made to establish the findings in lower animals, as holding good in man.

ACTION OF OPIUM ALKALOIDS

In respect to their chemical structure, the principal opium alkaloids may be divided into two groups. On the one hand we have the pyridin-phenanthrene group, characterized by the following grouping, and of which morphin and codein (methyl-morphin) are the principal members. On the other hand, we have the benzyl isoquinoline group, characterized by the other diagram, and of which the principal members are narcotin and papaverin.

Fig. 1. Pyridin-Phenanthrene Nucleus

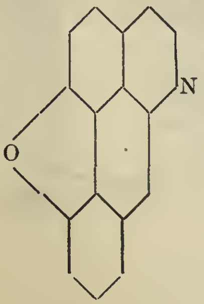
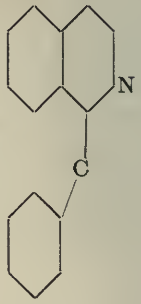


Fig. 2. Benzyl-Isoquinoline Nucleus



In respect to their pharmacological action the opium alkaloids can also be divided into the same two classes, the morphin and papaverin groups.

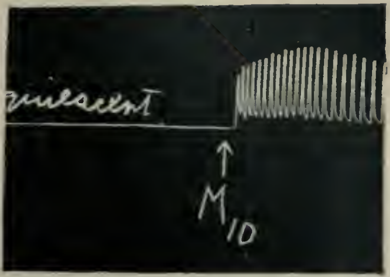


FIG. 3. RING OF PIG'S URETER

Twenty-four hours old. Quiescent. 10 mgm. of morphin start powerful contractions.

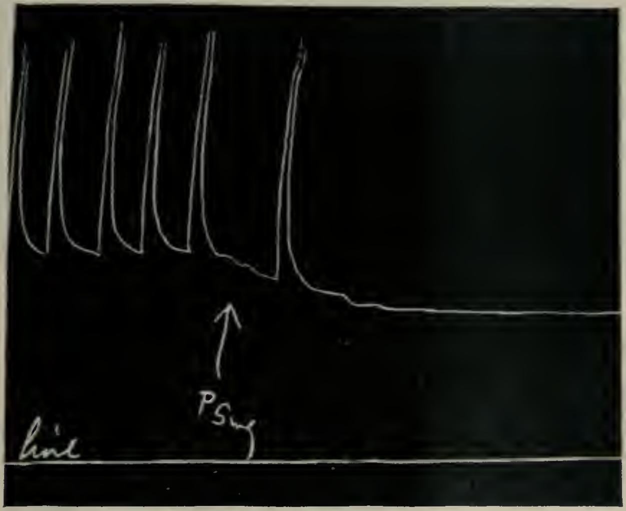


FIG. 4. PIG'S URETER

Showing effect of papaverin hydrochloride, 5 mgm. in 50 cc. Locke solution.

The effect of morphin on the ureteral ring is to *increase* its tonicity and the frequency of its contractions. This is precisely analogous to the effect of morphin on the intestinal smooth muscle strips, as shown by Magnus (5), Pal (6), Popper (7), and others. On the other hand, the effect of papaverin on the ureteral rings, as well as on other smooth muscle structures is to *relax* the tonus and slow or stop the contractions (8). These effects are illustrated by figures 3 and 4.

The effect of narcotin is very much the same. Both papaverin and narcotin produce results in this respect similar to that given by chloroform (fig. 5).

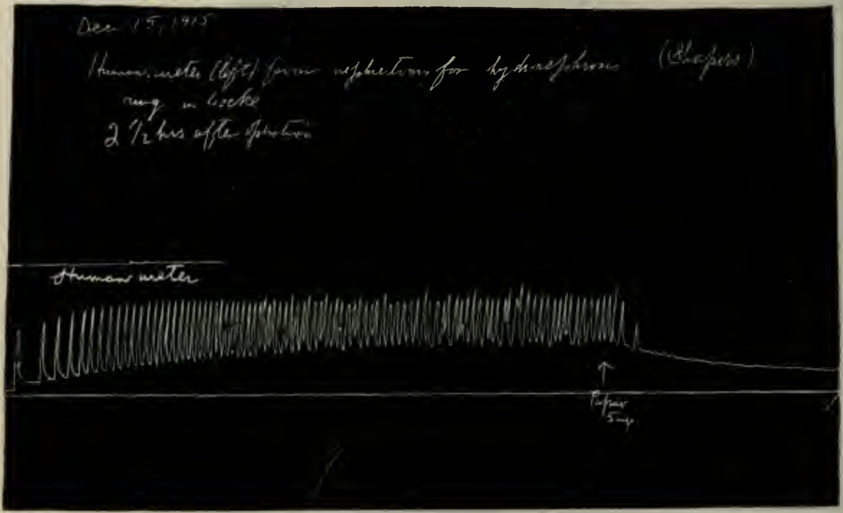


FIG. 5. HUMAN URETER, AFTER NEPHRECTOMY

Showing effect of papaverin. 5 mgs.

The action of opium or of a combination of all the opium alkaloids, such as for instance that of Sahli (9), is a resultant of the sum of its component effects. Now, it was found that a very small quantity of papaverin is sufficient to overcome the stimulating action of morphin on the ureter, and it was therefore not at all surprising to find that Sahli's combination of total opium alkaloids contained enough benzyl-isoquinoline derivatives to overbalance the local morphin effect, and produce relaxation of the ureteral ring and cessation of its contractions (fig. 6).

In order to ascertain whether the same conditions hold good in the intact animal, observations were made on the effect of morphin, and Sahli's combination on the intact ureters in rabbits with the same results as will be seen in the following protocols.

Experiment. June 20, 1916. Male rabbit, 1150 grams. Anæsthetized with paraldehyde, placed on warm table, and abdomen opened. Ureters were inspected at frequent intervals, for short periods at a time to avoid chilling.

12.15 p.m. Normal contractions: Right ureter contracts one time in a minute; left, two times in a minute. Intestinal peristalsis, active. Bladder full. Respirations 60 per minute.

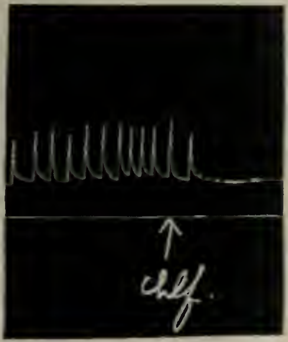


FIG. 6. RING OF PIG'S URETER
Showing effect of chloroform.

12.30 p.m. Injected in ear-vein 3 mgm. of morphin sulphate.

12.40 p.m. Right ureter contracts two to three times a minute; left, four times a minute. Intestinal peristalsis is active, if anything it is increased. Bladder is spasmodically contracted as can be seen and felt. Respirations are 48 per minute.

Experiment. June 22, 1916. Male rabbit, 1300 grams. Anæsthetized with paraldehyde and prepared same as above.

12.25 p.m. Right ureter contracts four times a minute; left three times a minute.

12.35 p.m. Right ureter contracts four times a minute; left, three times a minute. Respiration 72 per minute. Bladder full. Intestinal peristalsis active.

12.40 p.m. Injected in ear vein 4 mgm of Sahli's combination of total opium alkaloids (= morphin 2 mgms.)

12.45 p.m. Right ureter contracts three times a minute; left, two times a minute. Respirations 72 per minute. No spasm of bladder. Intestinal peristalsis less active.

12.47 p.m. Injected 6 mgm. more of Sahli's mixture (= morphin 3 mgm.).

12.50 p.m. Right ureter contracts, two times a minute; left, one time a minute. The contractions are visibly not as powerful as normal. Respirations 72 per minute. No spasm of bladder. Intestinal peristalsis very sluggish.

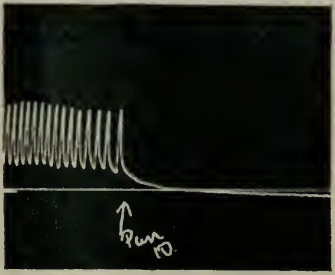


Fig. 7. Ring of Pig's Ureter

Showing the relaxing effect of 10 mgm. of Sahli's combination (= 5 mgm. morphin).

Finally, experiments with the same drugs and rings of human ureter from a case of nephrectomy were made, and fully corroborated the above findings (fig. 7).

DISCUSSION

From the above experiments it is clear that morphin alone, and morphin in combination with other opium alkaloids, produces different local effects upon the ureter. The alkaloid alone increases its tonus and contractions, whereas a combination of the total opium alkaloids causes a lowering of the tonus and an inhibition of the peristaltic movements. The practical interest of this observation is obvious. The local effect of morphin in ureteral colic is to increase the ureteral spasm—a very undesirable condition. This local spasmodic action on the ureter can be overcome by combining the morphin with papaverin or narcotin, or still better by administering the total opium alkaloids in the form of opium or of a combination like Sahli's. Such a combination meets admirably the required conditions. It relaxes the spasm, while at the same time, as has been shown by the author, it is actually more analgesic (10), less depressant to the respiration (11), and produces less nausea (12).

In order to antagonize the spasmodic effect of morphin, the exhibition of atropin naturally suggests itself. Experiments with combinations of morphin and atropin have shown, however, that the ordinary safe doses of atropin (not more than 1 mgm.) are insufficient to overcome the tonic effect of morphin (fig. 8).

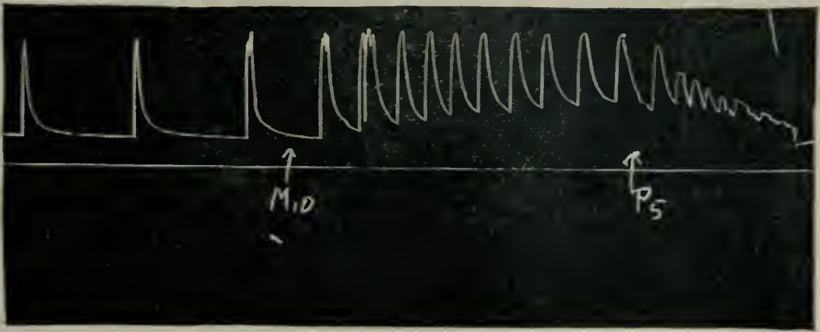


Fig. 8. Human Ureter. One Ring

From a nephrectomy for tumor of kidney. Two hours after operation, normal contractions one in one and one-half minute. Morphin 10 mgm. increases the frequency and tonus. Addition of papaverin hydrochloride 5 mgm. antagonizes the morphin effect. (June 28, 1916).

The practical application of the deductions drawn from the above experiments are well illustrated by the following case history.

B.U.I. 5072. Harry M., age 35; single; white; salesman. Admitted May 2, 1916. Diagnosis, ureteral calculus. Patient has in the past two years had two attacks of ureteral colic. This is the third attack. On admission patient was in agony and about 10 a.m. a hypodermic injection of morphin sulphate $\frac{1}{6}$ grain was given. Pain was not relieved, but vomiting was produced. About two hours later, an injection of $\frac{1}{4}$ grain of Sahli's mixture (=morphin $\frac{1}{8}$ grain) was given. The pain was quickly relieved, and no nausea was produced. The patient felt well and left the hospital next day, declining to undergo operation.

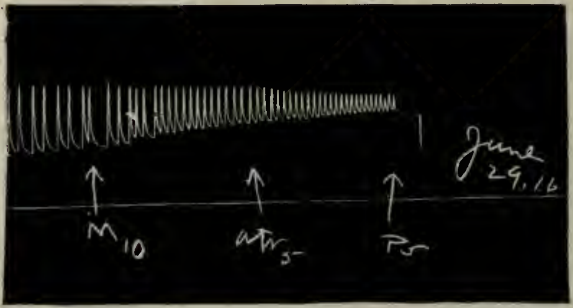


Fig. 9. Pig's Ureter. One Ring

Showing increase in contractions and tonus produced by 10 mgm. of morphin sulphate; addition of 5 mgm. of atropin sulphate does not overcome this stimulation, yet 5 mgm. is far in excess of any therapeutic dose in man (= $\frac{1}{24}$ grain). On other hand 5 mgm. of papaverin (P_5) causes immediate relaxation.

CONCLUSIONS[1]

1. Morphin produces an increase in tonicity and in the rate of contractions of the ureter.

2. Papaverin and narcotin produce a relaxation of the tonus of the ureter and an inhibition of its contractions.

3. Opium and other combinations of total opium alkaloids contain enough papaverin and narcotin to overcome the spasmodic local effect of morphin, and are therefore to be preferred to morphin in case of ureteral colic.

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[1] The full data of this investigation will appear in the Journal of Pharmacology and Experimental Therapeutics.

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THE GROWTH OF BACILLUS COLI IN URINE AT VARYING HYDROGEN ION CONCENTRATIONS

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INTRODUCTION

The present study was undertaken to determine the effects of accurately measured increases in acidity and alkalinity on the growth of B. coli. It was our hope to find inhibition within physiological limits which might be used as an aid in the treatment of pyelitis and cystitis. But it is equally important to know what the probable growth would be—within these limits—for any given reaction.

HISTORICAL

Pasteur (1879) noted the effects of acidity in culture media on microbial life (cit. Clark and Lubs 1917). Koch (1881) was the first to use acids and alkalies as germicides—and Kitasato (1888) was the first to make quantitative experiments. He determined the amount of hydrochloric, sulphuric and nitric acids, potassium iodide, bromide and chlorides necessary to kill, inhibit and allow normal growth of cholera and typhoid organisms. Behring (1890) and Boer (1890) were the first to use equimolar solutions (gram molecular equivalents per liter) to determine toxicity for pathogenic bacteria. Wüthrich (1892) following the advice of DeVries (1884) (there cited) used molar solutions of acids to study their effects on fungi spores. According to modern chemical views, solutions of acids, bases and salts are called electrolytes because they act as conductors of electricity. In water solutions they dissociate into their respective ions, each bearing a positive or negative charge. To Dreser (1893) belongs the credit for having shown that physiological action may depend on ionization. He worked with mercury salts and proved that the double hyposulphite of mercury and potassium, which on dissociation did not give Hg^{++} (mercury ions) was less toxic to yeasts, frogs and fishes, than the ionized mercury salts—as mercuric chloride. Paul and Krönig (1896) and Krönig and Paul (1897) did the classic work on the ionic effects of acids, bases and salts in their disinfecting power on anthrax spores and on Micrococcus aureus. This work has stood as a model for many subsequent investigations. Kahlenberg and True (1896) made an independent research on the effects of ions on the growth of higher plants, using Lupinus albus. They say (p. 123) "That the modern theory of solutions would throw light on their physiological action was to be expected. From the foregoing detailed results, it is evident that in the case of plants the toxic action of solutions of electrolytes when dissociation is practically complete is due to the action of the ions present. When dissociation is not complete the undissociated part may also exert a toxic effect—as has been pointed out in several instances. We have, then, as it were, a recognition of the theory of electrolytic dissociation by the organic world." Both Paul and Kahlenberg were students of Ostwald. Bial (1896) (1897) (1902) showed how the fermentation of yeasts was inhibited by acids and their salts. He became interested from the point of view of gastric acidity and its effects on fermentation. (A review of the antiseptic action of gastric juice with the literature on the subject is found in Gregersen (1916).) An excellent review of the work of these three investigators together with that of other earlier investigators will be found in the article by Winslow and Lochridge (1906). Their contribution dealt with the amount of hydrochloric, sulphuric, benzoic and acetic acids expressed as normality, in parts of acid per million, total hydrogen per million, and H^+[1] per million necessary to kill B. coli and B. typhi in forty minutes at room temperature. They also show what percentage was killed by smaller amounts of acid. Their figures show the effect of acids in tap water but when peptone was introduced they could not quantitate their results except by a rough comparison to conductivity. This was according to the best data available at that time. The specific ionic effect of H^+ became very rapidly applied to biology. (See bibliography for further references.) Further development has come from a knowledge of the laws governing the acidity of solutions developed largely in this country by Henderson (1908) (1909) (1911) (1913) and abroad by Sörenson (1909) (1912), Friedenthal, and Michaelis (1914). For an excellent discussion of p_H especially in relation to the field of bacteriology we are indebted to Clark and Clark and Lubs (1915) (1916) (1917).

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[1] $H+$ means hydrogen ions; p_H means hydrogen ion concentration.

The modern physiological conception of acidity and alkalinity depends on the relation between the hydrogen ions $(H)^+$ and hydroxyl ions $(OH)^-$. If they are equal in number the solution is neutral. This is the case with water. It can be represented by the following formula:

$$H_2O = (H)^+ + (OH)^-$$

and in neutral solution, as in water

$$(H)^+ = (OH)^-$$

By various methods the value of H in this equation = 0.0000001 gram per liter or 1×10^{-7} or as expressed by Sörenson p_H = 7.0. Thus, in terms used in this paper, p_H 7.0 represents neutrality. Numbers larger than p 7.0 represent alkalinity; numbers smaller represent acidity. The order of magnitude of the changes used in this paper can easily be borne in mind when we realize that tap water boiled and cooled may vary from p_H 5.0 to 8.0, urine from p_H 4.7 to 8.7 (Palmer and Henderson, 1913), and culture media probably as widely, depending on the care and the methods by which they are made. Thus we can see ample practical justification for following Clark and Hurwitz in carefully regulating the reaction of culture media.

Henderson and Webster (1907) suggested using for bacteriologic studies media in which neutrality could be maintained by phosphates. Michaelis and Marcora (1912) determined the p_H of cultures of coli by the electrical method and found they produced acid until they reached a final or limiting p_H, which was about 1×10^{-5} or p_H 5.0. They also inoculated acetate mixtures of known p_H and found good growth at 1×10^{-5} (p_H 5.0), 100 colonies at 2×10^{-5} (p_H 4.7), 50 colonies at 4×10^{-5} (p_H 4.4) and none at 8×10^{-5} (p_H 4.1) or in any more acid media. Clark and Lubs (1915) used the final p_H as a means of differentiating the groups of B. coli. Ayres (1916) has applied this same method to a study of streptococci. Bruenn, (1913) a pupil of Michaelis, has used mixtures of definite p_H to determine the effect of acid as a disinfectant for B. coli and B. typhi. He comes to the conclusion that, independent of the concentration of the mixture of acid and salt, and using lactates as well as acetates, the disinfection is dependent upon the p_H. He found that the death point varied between p_H 2×10^{-5} and 4×10^{-5} (p_H 4.7 – 4.4) for coli, and from p_H 0.25×10^{-5}, to 1×10^{-5} or 2×10^{-5} (p_H 5.6 – 5.0 –4.7) for typhoid. Lately, Norton and Hsu (1916) have also shown the effect of p_H on the killing of B. typhosus (Hopkins) using formic acid and formic acid-ammonium formate mixtures. They took as their standard the p_H necessary to kill 9,000,000 organisms at 20° in a few minutes to several hours. 6×10^{-3} (p_H 2.2) killed in five minutes and 2×10^{-3} (p_H 2.7) killed in two hundred minutes. From this they calculate that the disinfecting power is porportional to the p_H, and that acid ions are positive catalysers, and the undissociated acid negative catalysers in acid disinfection. They promise further investigations as to the mechanism of the salt action.

If we had merely been interested in the killing of B. coli and its relation to hydrogen ion concentration, our work would only have been confirmatory. However, what we wanted was, not the p_H which kills many organisms in a short time but one which would inhibit their growth within the body. Furthermore, we were equally if not more interested in two other things, namely, the point on the alkaline side at which we could observe an inhibition, and the probable expectancy of growth at varying degrees of acidity—a biological curve of the mean, mode and limits of growth with regard to acidity. Quinby (1917) has outlined the advisability of such investigations but so far we know of no literature in modern terms bearing on these points.

EXPERIMENTAL

B. coli was chosen (1) because it is commonly used for work in disinfection ; (2) because it is the commonest organism found in pyelitis and cases after instrumentation; and (3) because we had reason to believe that it was in many respects the hardiest of the organisms commonly found in the genito-urinary tract.

The organisms were grown on agar and transferred to bouillon. This was very nearly neutral (p_H 7.0) (see Clark (1915)). It was tested before making an inoculation and was rejected if more acid than p_H 6.8—or more alkaline than p_H 7.2. A twenty-four-hour bouillon culture was used unless otherwise mentioned.

The urine was obtained without instrumentation. We rejected the first portion so as to irrigate the anterior urethra and caught the rest in a sterile flask. It was plated without dilution and rejected if not sterile. Ten cubic centimeter aliquot portions were titrated with n/10 NaOH and n/10 HCl to the desired p_H from 114.6 – 9.6 by the colorimetric method (Clark and Lubs) (1917). To determine the p_H of the solution, use was made of standards made up of acid potassium phthalate, phosphates and borates. The following indicators were used:[2]

p_H 4.4–5.6 Methyl red
p_H 5.6–6.8 Dibrom *o*-cresol sulphonephthalein
p_H 6.8–8.0 Phenol sulphonephthalein
p_H 7.2–8.8 *o*-cresol sulphonephthalein
p_H 8.0–9.6 Thymol sulphonephthalein

The required amount of acid or alkali was added to 10 cc. of sterile urine in large test tubes, so that the total amount and concentration of salts should be uniform.

As an illustration of the method, we will suppose that it is desired to add to the urine (a) 5 cc. of alkali, (b) 3 cc. of alkali, and (c) 1 cc. of acid. In the first case, of course, 5 cc. of alkali solution would be taken, but in the second, 4 cc. of alkali and 1 cc. of acid and in the third 2 cc. of alkali and 3 cc. of acid. Thus in every case 5 cc. of solution was added to the urine. Acid and alkali of the strength used are sterile and we have not obtained contamination in controls using this technique. At the end of the day we again tested the p_H and found this had not changed more than 0.3 p_H, generally less than 0.2 p_H from the original titer.

The tubes were then inoculated with one standard loop or 0.0001 cc. of the culture, in either case about 50,000 of the organisms being present. They were incubated at 37.0°C. At definite periods following 1 cc. of the contents was removed by a sterile pipette. Care was taken to mix the fluid thoroughly before taking the sample. This was then diluted in sterile salt solution in 99 cc. flasks and 9 cc. tubes, from one ten-thousandth to one ten-millionth as indicated. A clean sterile pipette was used for each dilution. One cubic centimeter was then put into agar (kept in a bath at 42°C.) and plated. The number of colonies was counted after growing at 37° for thirty-six hours to forty-eight hours. We always used two or three dilutions of each sample. This acted as a check and also gave us plates which could be readily counted. All colonies were counted up to 500 on each plate. Above this we estimated the number by counting two-tenths to four-tenths of the plate. The procedure was made as uniform as possible so that either of us might make a series, one set of dilutions or a part of one. We could not distinguish between the series so made.

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[2] The sulphonephthalein indicators can be obtained from Hynson, Westcott and Dunning, Baltimore.

RESULTS

The table of results will be found at the end of the article. (Table I).

The results have been plotted in two ways: first each curve representing those organisms growing at a given p_H, plotting number of colonies as ordinates and time as abscissae, and second, the number of organisms grown in a varying number of hours—plotting as before the number of colonies as ordinates but p_H as abscissae. A glance at the first curve (fig. 1) which is a typical example, shows that very small changes in the reaction of the medium in which the organisms grow cause marked differences in the amount of growth. The organisms are sensitive to a demonstrable degree to changes of 0.2 on the p_H scale. Fig. 2 shows the limits and the optima of growth. The organisms of the colon type are inhibited in growth at about p_H 4.6 to 5.0 on the acid side and p_H 9.2 go 9.6 on the alkaline side. The optimum reaction is that which approximates true neutrality or 7.0 but is roughly between 6.0 to 7.0. This is the average reaction of the urine of a person on a mixed diet.

The staphylococci show apparently the same range as the coli.

The streptococcus was obtained from a patient, who, prior to his entrance to the hospital had been treated without relief with alkali and in sufficient amount to keep his urine alkaline (to litmus). This organism shows an unusually alkaline range.

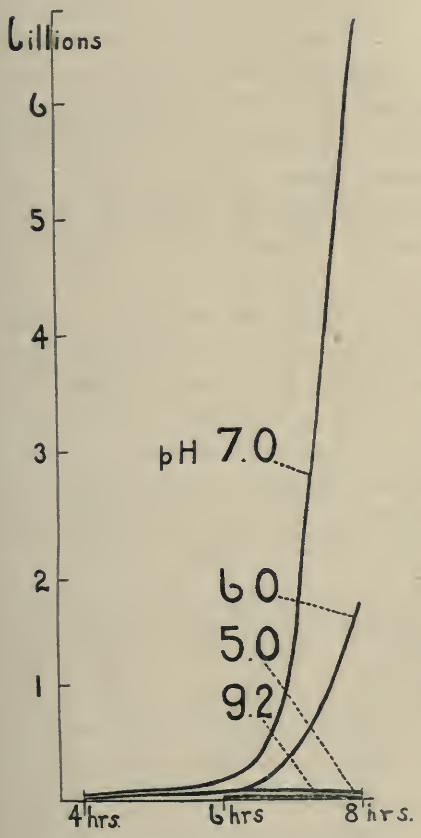

Fig. 1. Coli 50

Number of organisms in billions, per cubic centimeter of urine, incubated at 37°C. at given p_H.

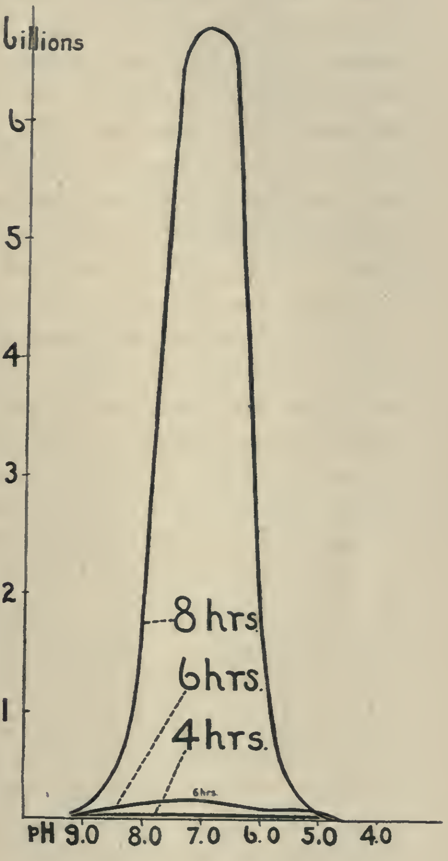

Fig. 2. Coli 50

Number of organisms in billions, per cubic centimeter of urine, incubated at 37°C. at a given time.

The typhoid organism shows a smaller range than any and within easy range of the possible variation of the normal urine.

DISCUSSION

We feel that the distinction made by Kitasato (1888) (1889) is a valuable one in the present connection. He mentions (a) the amount necessary to kill, (b) to inhibit growth, (c) to allow normal growth. This was also done by Boer (1890), who showed that inhibited organisms were still capable of growth when reinoculated into bouillon. We were able to show the same phenomenon by adding acid to the alkaline cultures and alkali to the acid ones and getting growth where there was none before. Wüthrich (1892) also gave the figures for normal, inhibition and death. Clark (1899) gave four classes (1) death, (2) inhibition, (3) injury, (4) normal.

For our purposes the figures are (1) death, (2) inhibition, (3) final p_H—Clark and Lubs,[3] (4) optimum. It is interesting to note from Michaelis and Marcora (1912) how near the death point and the inhibition point are. This is of course a function of many variables, among others the rate of disinfection, the temperature effect, on both the disinfecting power and the growth. A discussion of these factors would take us too far but the papers of Chick (1908) (1910), Madsen and Nyman (1908), Paul Bierstein and Reuss (1910), and Norton and Hsu (1916) throw great light upon it. It is of especial interest in a problem of mixed infection such as Luxwolda (1912) has worked out. In this article it was a question of what organisms would survive in milk at varying temperatures, and it was desired to have the acid-producing organisms inhibit the growth of the putrefying organisms. According to Clark (1915), Clark and Lubs (1915) and Michaelis and Marcora (1912) the organisms reached a limiting acidity. If coli are grown in a sugar-free bouillon it will become alkaline and in about 50 cultures this has been very close to p_H 8.4. In urine, however, the final p_H at the end of several weeks is very near the original one, for coli. It becomes more alkaline in acid urine and more acid in alkaline urine.

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[3] The final p_H on Clark and Lubs media has been incorporated into the criteria for separating the colon group by the Committee of the American Society of Bacteriology. An acid p_H goes with "low ratio organisms" $\left(\frac{CO_2}{H_2}\right)$ and the more alkaline ones with the "high ratio organisms." Winslow and Kligler (1916).

Our conditions, the number of bacteria, the reaction and temperature, have been taken because they were favorable to growth.

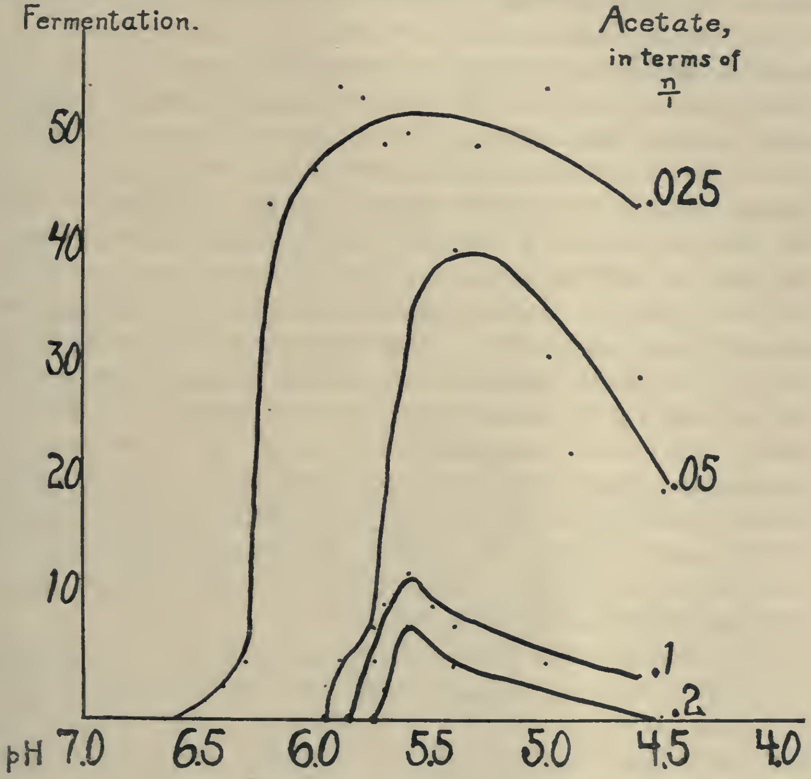

Fig. 3. Bial's Data on Fermentation of Yeast at Given Concentration of Acetate Mixture, Figured in Terms of p_H.

0.25 gram of yeast used with 0.025 n/1 acetate mixture, and with 0.05 n/1 acetate mixture. 0.5 gram used with 0.1 n/1 acetate (figures reduced to one-half) 1 gram used with 0.2 n/1 acetate (figures reduced to one-fourth). 60 means complete fermentation.

The medium was chosen for the same reason. The latent period as recently described by Chesney (1916) is amply shown in our results. We observed, however, a longer latent period in urine than in bouillon. Urine is not only easy to regulate as to reaction, but it contains enough nitrogen as urea, α-amino acid nitrogen (Rettger, Berman and Sturges, 1916) ammonia, and xanthine bases for growth. The lipoids and vitamines would also be sufficient. It is favorable as to salt concentration. This was not the case with Bial (1902, p. 524); with increasing amounts of acetates he decreased the fermentation. We must remember that his was a more delicate measure than ours—a cessation or impairment of function. We have appended a chart which we have compiled from his data (experiments 16, 17, 18, 19), (fig. 3). His figures can be expressed in terms of p_H since they are the acetate mixtures studed by Walpole (1914). Hägglund (1914) has studied the yeasts from this point of view and has shown the effect of different temperatures and different p_H, but he did not, unfortunately, choose conditions to show either the optimum or the concentration effect. Bial's figures show, as could be expected, that yeasts grow in a more acid medium than B. coli. The optimum is evidently near p_H 5.0 with an alkaline inhibition near p 7.0 and an acid inhibition near p_H 4.0 (?) With an increasing salt content there is a salt antisepsis. This apparently has not much effect on bacteria, as Bruenn (1913) showed he could take five times or one-fifth the concentration with the same effect. Dilution of urine one-half and one-tenth caused very slight changes in the growth.

Our figures p_H 4.6 to 5.0 agree very well with those of Michaelis (1912) 1×10^{-5} (p_H 5.0) and Clark (1915) p_H 46.–4.8 and Clark and Lubs (1915) p_H 4.9 to 5.1 for the acid inhibition of B. coli and corroborate their findings. It is almost impossible to draw any conclusions from comparison with Winslow and Lochridge's (1906) figures. They found 7 to 10 parts per million (p_H 3.0 to 3.6) for the amount of acid to kill 100 per cent of organisms at room temperature in forty minutes. The same applies to the results of Norton and Hsu (1916), $H^+ 3.4 \times 10^{-3}$ (p_H 2.5) to kill in fifteen minutes, 2.6×10^{-3} (p_H 2.6) to kill in two hundred and five minutes.

It is, of course, very difficult to obtain accurate results in dilute solutions that have no buffer value. The bacteria themselves may have enough salt or phosphate to change very appreciably the reaction. Michaelis and Adler (1914) have shown that when controlled by the H^+ electrode solutions of $\frac{HCl}{NaCl}$ of the same p_H give the same values in biological systems as any other source of H^+. All these figures are, however, of the same order of magnitude. All figures in which fixed quantities of acids or alkalies have been added to gelatine or bouillon previously neutralized to phenolphthalein must be rejected, for as Clark (1915) has shown, we cannot calculate the true reaction.

Many organisms require special media made from body fluids, such as hydrocele fluid, ascitic fluid and blood serum. Henderson (1909b) has shown how the body fluids are kept at neutrality with a remarkable constancy. These special media probably act partly through maintaining the body reaction, for neutrality is the optimum for growth.

We hope to continue the study of these problems, especially in the application of these findings to clinical problems.

SUMMARY

1. B. coli are inhibited from growing in urine at p 4.6 to 5.0 on the acid side, 9.2 to 9.6 on the alkaline side.
2. Typhoid (Rawlings) has narrower limits.
3. The optimum for growth of coli lies at p_H 6.0 to 7.0.

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It has been considered worth while to append a comprehensive list of references of this subject.

TABLE 1

Number of organisms per cubic centimeter of urine. Initial number equals 5000 per cubic centimeter. Urine titrated to p_H indicated. Incubated at 37°C.

ORGANISM	P_H	4 HOURS	6 HOURS	8 HOURS	10 HOURS	12 HOURS
Coli aab	5.0	20,000	50,000	0	0	
	5.9	300,000	1,000,000	35,000,000	53,000,000	
	9.0	30,000	1,200,000	14,000,000	50,000,000	
	5.6	1,100,000	34,000,000	190,000,000	170,000,000	210,000,000
	7.4	4,500,000	∞	180,000,000	460,000,000	∞
	9.6	10,000	30,000	4,000,000	19,000,000	
Coli zv	5.0	1,100,000	12,000,000	30,000,000	32,000,000	
	5.45	1,700,000	14,500,000	97,000,000	68,000,000	
	6.8	2,700,000	45,000,000	212,000,000	129,000,000	
	7.8	1,900,000	26,000,000	126,000,000	105,000,000	
	8.8	700,000	11,000,000	70,000,000	62,000,000	
	4.8	22,500,000	55,000,000	49,000,000		
	7.0	60,000,000	300,000,000	200,000,000		
	7.4	80,000,000	280,000,000	230,000,000		
	9.2	35,000,000	140,000,000	90,000,000		
	9.6	0	0	0		
	4.6	160,000	200,000	900,000	16,000,000	
	9.4	30,000	0	40,000	0	
Coli ze	5.0	3,600,000	9,600,000	58,000,000	70,000,000	
	5.8	7,700,000	55,000,000	255,000,000	195,000,000	
	6.8	17,400,000	68,000,000	330,000,000	530,000,000	
	7.8	12,500,000	69,000,000	610,000,000	1,250,000,000	
	8.8	2,200,000	10,500,000	200,000,000	300,000,000	
	4.6	400,000	1,400,000	22,300,000	28,000,000	
	4.8	800,000	11,900,000	26,000,000	66,000,000	
	9.4	400,000	0	0	10,000	
Coli yv	4.6	5,200,000	30,000,000	46,000,000	60,000,000	
	9.2	200,000	170,000	1,500,000	13,000,000	
	5.8	2,000,000	92,000,000	230,000,000	420,000,000	740,000,000
	7.0	1,900,000	93,000,000	195,000,000	395,000,000	760,000,000
	8.0	2,000,000	61,000,000	170,000,000	210,000,000	500,000,000
	9.4	100,000	500,000	3,600,000	39,000,000	130,000,000

TABLE 1—Continued

ORGANISM	P_H	4 HOURS	6 HOURS	8 HOURS	10 HOURS	12 HOURS
Coli bu	4.6	180,000	480,000		6,500,000	
	5.0	1,900,000	44,000,000		280,000,000	
	6.0	11,800,000	500,000,000		3,150,000,000	
	7.0	36,400,000	130,000,000		125,000,000	
	9.2	7,600,000	55,000,000		∞	
	9.6	80,000	10,000		0	
	5.5		500,000,000	3,700,000,000	8,900,000,000	
	6.0		400,000,000	3,900,000,000	9,999,000,000	
	6.7		590,000,000	4,500,000,000	3,700,000,000	
	7.4		620,000,000	4,300,000,000	3,700,000,000	
Coli 50	4.6	20,000	0	0		
	5.0	1,200,000	78,000,000	50,000,000		
	6.0	13,000,000	100,000,000	1,680,000,000		
	7.0	20,000,000	150,000,000	6,700,000,000		
	9.2	60,000	200,000	11,600,000		
	9.6	0	10,000	200,000		
Typhoid (Rawlings)	4.6	0	0	0	0	
	5.0	0	0	0	0	
	6.4	300,000	2,000,000	20,000,000	470,000,000	
	7.4	100,000	2,000,000	6,000,000	50,000,000	
	8.8	10,000	0	0	0	
	9.2	10,000	0	0	0	
Staph. Aureus	4.6	30,000	400,000	1,100,000	12,700,000	
	7.0	4,200,000	18,000,000	140,000,000	200,000,000	
	9.2	400,000	2,700,000	15,000,000	31,000,000	
	8.0	300,000	13,200,000	43,000,000	55,000,000	88,000,000
	9.4	300,000	800,000	3,700,000	13,000,000	35,000,000
Staph. Albus	4.6	100,000	200,000	10,000	0	
	5.5	100,000	2,400,000	47,000,000	69,000,000	
	6.4	600,000	6,600,000	104,000,000	63,000,000	
	7.4	600,000	7,900,000	80,000,000	70,000,000	
	8.4	900,000	6,400,000	27,000,000	35,000,000	
	9.4	0	20,000	600,000	1,500,000	
Strep. h.	4.6	40,000	10,000		0	
	5.0	90,000	10,000		300,000	
	6.0	300,000	650,000		6,700,000	
	7.0	1,100,000	2,900,000		15,000,000	
	9.2	950,000	2,300,000		55,000,000	
	9.6	220,000	1,600,000		40,500,000	

∞ Indicates many organisms—not counted.

TABLE 1—Concluded

Characteristics of the organisms

NAME	DEXTROSE	SACCHAROSE	RAFFINOSE	ADONITE	DULCITE	LACTOSE	$\frac{Co_2}{H_2}$	LIMITING P_H C & L MEDIA
aab[1]	+	−	−	−	−	+	1.06	5.1
zv[1]	+	+	+	−	−	+	1.06	4.9
ze[1]	+	+	+	+	+	+	2.40	6.8
yv[1]	+	−	+	+	+	+	2.07	6.8
bu[2]*	+	+				+		5.0
50[2]*	+	+				+		4.9
Typh.[2]† (Rawlings)								
Staphylococcus alb.[2]†								
Staphylococcus Aureus[2]*								
Streptococcus[3]*								

[1] Obtained from Drs. Clark and Lubs.

[2] Obtained from Dr. Bayne-Jones.

[3] Obtained from Harriet Lane Home.

* Pyelitis case.

† Stock culture.

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THE VERUMONTANUM, WITH SPECIAL REFERENCE TO THE SINUS POCULARIS: ITS ANATOMY, HISTOLOGY, AND PHYSIOLOGY

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In 1914 I reported before the Genito-Urinary Section of the American Medical Association a new instrument for the radical removal of the verumontanum and discussed briefly the anatomy, histology and pathology of this organ based on studies of specimens removed by this operation. Since this time, the question has been pursued further using for the purpose serial sections of the entire verumontanum obtained at autopsies. As a result of this more advanced study, I am able to add somewhat to my previous report and am compelled to make a few minor corrections of views expressed in the former paper concerning its histology. In the report alluded to, the verumontanum was described as composed of a central glandular and peripheral stromal portion and the sinus pocularis as a long canal lined by a many layered squamous epithelium and ending in a complicating system of invagination processes. The central group of glands was described as surrounding the sinus pocularis. Up to this time I had not determined the manner by which these glands emptied themselves. It was only after making many sections of the entire verumontanum and including all the sections in the study that it was possible to clear up this point. My first studies included about eighteen specimens removed by operation. Of these only three were cut serially and every fifth section was only utilized. As a result I missed completely the outlet of these glands and began to think of ductless glands, internal secretion, etc., because, their structure was one which suggested activity of some sort. However, after making the sections extremely thin and studying every section very carefully it was learned that these glands emptied by smaller and larger ducts into the very large duct or long canal which I considered the entire sinus pocularis. In other words, the sinus pocularis is a highly glandular organ composed of numerous acini, which open by smaller and larger ducts into one grand or common duct and this in turn opens on the surface of the verumontanum by a rounded or slit-like opening. In my previous study I missed the connecting link, namely, the small ducts between the central groups of glands and the grand or common duct. This caused me to re-arrange my conception of the sinus pocularis and not only to study its histology with more interest, which will be described anew and more completely, but to learn how the older anatomists regarded it, especially E. H. Weber, who called it the uterus masculinus.

HISTORICAL

Among urologists at the present time, a great deal of interest is manifested in the verumontanum on account of the important rôle its pathology is supposed to play in the production of many sexual disturbances, so commonly seen in the male. A large number of modern text-books on embryology, histology, anatomy, pathology, and genito-urinary surgery have been examined and it was surprising to find what a dearth of information there was on the subject of the verumontanum. If we go back to the older literature, we find a more generous discussion of the anatomy of this organ, but the consideration of its histology is scant and for the most part so inaccurate, that it was of little use for the purpose of this study. The best description perhaps that can be found in the older literature is that by Rüdinger. Henle in his text-book on anatomy has devoted considerable space to this organ. In some instances, we will find a rather elaborate description of the verumontanum, but it is surprising to learn after a study of this organ how inaccurate are such descriptions.

Weber in 1836 described more accurately the meaning of the vesiculae prostaticae in men and at the Research Convention of Naturalists in Braunschweig in 1841 laid before them his observation of the uterus masculinus in mammals. He discussed the organ and the relationship of its position and form in rabbits, horses, dogs, hogs, the cat, and humans.

Weber looked upon the sinus pocularis as an embryonic rest and regarded it as corresponding to the female uterus, on which account, he called it the uterus masculinus. It has also been called the organ of Weber, after this same author, giving the mpression that it was first described by him. However, it was first described and illustrated by Morgagni under the name of "sinus prostatae" and later by Albinus and Schlichting. Severinus mentions the structure by the name of sinus prostatae and gives an indefinite drawing of it in the Circopithecus, but as he does not add any particular description of it, it is impossible to know what he means by sinus prostatae. Luckhart briefly described the uterus masculinus in various animals. Ackermann found it in an hypospadiac and describes it as an uterus under the name uterus cystoides, without, however, being aware of its normal occurrence. He mentions other examples by Petit, Sue and Maret. Pallas mentions that both ductuli deferentes in Leptus Ogotona open in one canal of which he gives a drawing. Meckel mentions it. Brandt and Ratzeburg have described the two horned uterus masculinus in mammals. Rathke found in his researches on the genital organs of sheep and pig embryos, a similarity of these portions of the different sections so marked that the male organ could be differentiated from the female only with difficulty. He was therefore the first to call attention to the analogy to the uterus of the male fetus, but he did not carry out his researches upon the adult animal. Of all these authors Weber has written the most, but his descriptions of it are more or less coarse and of no value in the present study. Rüdinger in 1883 described it more accurately and illustrated it with a number of drawings, but even his description was faulty and incomplete. Of the older clinicians, the chief ones to devote attention to it were Lallemand and Grünfeld, the latter having been the first to observe it urethroscopically. In this country clinical articles by Hawkins, Swinburne, Ruggles, Randall and others have appeared, in addition to an excellent article by Belfield on utriculitis in which the author discusses the embryology of the utricle and its pathological and clinical possibilities. Among the modern foreign writers, several clinical articles have appeared by Wossidlo, Orlowski, Luys and others.

VERUMONTANUM. SYNONYMS:—SCHNEPSENKOPF, COLLICULUS SEMINALIS, CORNUCULA SEMINALIS, CAPUT GALLINACEUM, CRISTA URETHRALIS

Anatomy. The verumontanum is a small, rounded, oval, elliptical, or conical elevation, situated on the floor of the proximal half of the posterior urethra. Its posterior surface is sharply demarcated from the floor of the posterior urethra, whereas its anterior surface tapers gradually off into the crista galli. Occasionally it tapers gradually posteriorly, as it always does anteriorly. Its color is a pale pink, and lighter in hue than the surrounding mucous membrane of the urethra. The verumontanum is separated from the prostate by the floor of the urethra and a few gland acini (suburethral group of glands). Posteriorly it extends upward and fades off insensibly in the floor of the vesical neck by a number (about six) of longitudinal striae. On its anterior surface in the mid line is an opening which is usually rounded, but may be slit-like or quarter-moon in shape and about one-eighth of an inch in length. This is the mouth of the sinus pocularis. At times the opening of the sinus pocularis may be found upon the superior rather than upon the anterior surface of the verumontanum. The base of the verumontanum is firmly attached to the wall of the urethra. The verumontanum could not be dissected entirely free of the urethra owing to its intimate connection therewith and the fact that the main structures composing it, namely, the sinus pocularis, the ejaculatory ducts and prostatic ducts, extend through the entire urethral wall and to the prostate below. Opening at a point in front, below, laterally or even posteriorly to the opening of the sinus pocularis and not necessarily bearing a symmetrical relation, as regards position or shape, are the ejaculatory ducts opening by mouths which may be rounded or slit-like, the latter straight or concave. The latter may be so small and so flat that they cannot be seen with the naked eye. Even in fresh specimens, it may be necessary to inject them before they can be recognized by the spurt which is in an upward direction. On the other hand they may be so prominent that they are larger than the opening of the sinus pocularis. The elevation is formed by the upward growth or extension of the sinus pocularis. In other words, remove from the verumontanum the sinus pocularis, the ejaculatory ducts and the prostatic ducts, and you will have a smooth flat surface remaining, even with the rest of the posterior urethra and possessing a structure identical to it.

SINUS POCULARIS. SYNONYMS:—UTRICULUS PROSTATICUS, VESICULA SPERMATICA SPURIA, VESICA PROSTATICA, WEBER UTERUS MASCULINUS, ORGAN OF WEBER

Definition. It is an encapsulated, glandular organ, whose acini open by smaller and larger ducts into one grand or common duct. The latter opens usually on the anterior surface of the verumontanum by an opening which is either a rounded aperture or straight or concave slit. The glandular acini are separated by an interglandular stroma, which is derived from and is continuous with the capsule or wall of the sinus pocularis.

Glandular acini structure. The glands vary in number, in size, and in shape in the various specimens. They may be simple, racemose glands or they may in some portions show rather marked intra-acinous proliferation (figs. 1, 4). The wall or base of the acini is composed of a flattened layer of connective tissue cells upon which are immediately apposed the cells of the acini themselves. The latter may be simple columnar or simple cuboidal in type, more often the latter (fig. 4). Occasionally, the cells of the acini are so closely packed, that they appear somewhat squamous in type. The number of cell layers, is usually two or three, although at times owing to the way the specimen has been sectioned, it will appear many layered. The nuclei are small sized, rather rounded in shape and usually take the stain well. The protoplasm is clear and also takes the eosin stain with avidity. The lumen of the glands seems empty, but occasionally corpora amylacea are seen in them (fig. 8). Exfoliated epithelium is also seen at times within their lumen. From the manner in which the gland cells take the stain and their appearance of activity, it is quite probable that they have some active function to perform. This is also evidenced by the fact that the walls of the acini show healthy, active looking tissue, not atrophic as it would presumably appear if the organ were only an embryonic rest.

Ducts. By thin serial sections, it is easy to see that these glandular acini open by smaller and larger ducts into one grand or common duct (figs. 1, 2). The latter courses obliquely throughout the entire length of the sinus pocularis and is lined, like the smaller ducts, with the same type of epithelium as the acini themselves. The invagination processes which I described in my previous paper simply represent larger ducts, emptying into the grand or common duct. In one specimen, the common duct, instead of coursing obliquely through the sinus pocularis, had a semilunar shape, capping the glandular portion, into which the latter emptied their contents. This gave the duct a rather bicornuate appearance (fig. 2). The glands of the sinus pocularis, encased in their firm capsule, are seen in every portion of the organ. The sinus pocularis ends either in the substance of the urethral wall or dips down slightly to end in the upper part of the basis prostatae.

Common duct. This duct courses usually in an oblique manner throughout the entire sinus pocularis and is lined by the same type of epithelium as the acini and on cross section looks like a mucous membrane with many invagination processes (figs. 1, 6). Serially, however, it can be seen that these invagination processes are the larger ducts which receive as tributaries the smaller ducts and which in turn drain the glands themselves (figs. 2, 6).

Capsule. The entire sinus pocularis is enclosed in a very firm wall or tunic which microscopically is composed principally of fibrous tissue with a generous admixture of smooth muscle fibers. By special staining I was able to show that it also contained elastic tissue (fig. 9). Lowsley claims that the verumontanum contains no elastic tissue. The wall of the sinus pocularis varies in thickness in its different portions. It is continuous with the interglandular stroma of the prostate and ends insensibly in the muscular wall of the urethra. By serial sections one can trace the interglandular stroma of the prostate and see how it forms the wall of the prostatic acini and from here dips in between the individual acini and forms their fine supporting framework. Similarly, it continues to form the wall of the sinus pocularis, whence it extends to form the supporting framework of its glandular acini. From here one can trace it to its insensible ending in the body of the urethral wall.

Physiology. The exact function of the verumontanum is not known. The old view was that it was composed of characteristic blood spaces and that during erection, these spaces filled and engorged the verumontanum to a size which caused a blockage of the posterior urethra and prevented regurgitation of semen during ejaculation. This view was first promulgated by Weber and subscribed to by Waldeyer, Frisch, Cobelt, Rüdinger, etc. First of all, the verumontanum is not composed of characteristic blood spaces. Indeed, the blood supply to it is not any richer than that of the surrounding tissues. If this contention were true, the radical removal of the verumontanum would be followed by regurgitation of semen into the bladder during ejaculation. The author has removed the verumontanum without ever noting this occurrence. Walker has summed up eleven objections to this view, namely:

> First: The verumontanum is not situated in the posterior portion of the prostatic urethra, but in the middle and anterior portions; so that, if the swelling were sufficient to block the urethra it would obliterate the whole cavity.
>
> Second: The caput gallinaceum is in the most capacious part of the prostatic urethra. It is not probable that an organ which was to act as an obstruction would be placed in a position which was most unfavorable for the performance of that function.
>
> Third: The urethral fold covering the organ is as vascular as the others; but the substance of the organ proper is much less so; and in several cases, pointed out by Rüdinger, it was very deficient in blood-vessels. It is, therefore, not vascular enough to produce the necessary swelling to strongly obliterate the urethra at this point.

Fourth: From the crest it generally slopes toward the membranous urethra, forming the crista urethralis anterior, and does not end more or less abruptly, as would be expected if it were intended to act as a valve. It is thus in a very poor mechanical condition to offer resistance, even if it were forcibly pressed against the anterior wall.

Fifth: The ejaculatory ducts empty on, or very near, the crest of the elevation, most of the prostatic ducts pouring out their secretion opposite or behind it, so that if it were sufficiently enlarged to obliterate the urethra, it would entirely close both prostatic and ejaculatory ducts.

Sixth: The corpora spongiosa, in the anterior portion of the urethra, offer the same kind of resistance; and to nearly, if not altogether, the same degree as the verumontanum. The congestion is even greater in the penile portions, for the venous return is prevented by muscular contraction.

Seventh: In the hedgehog and cat, the organ is placed considerably forward in the urethra, and between it and the bladder, the urethra is narrow, and surrounded by a thick muscular coat, which offers all the necessary resistance.

Eighth: A cast taken of the distended urethra shows the organ pushed into the anterior portion and it is, relatively, a very insignificant elevation.

Ninth: An artificial erection was made in a human cadaver by forcibly filling the blood vessels of penis, prostate, and bladder. During this, a low melting paraffin was injected into the urethra; under very slight pressure it passed directly into the bladder. After the bladder was quite full, the pelvis was cooled, and laid in strong muriatic acid, until the flesh was removed. The cast thus obtained showed a moderately capacious prostatic urethra, with the verumontanum extending not more than half way to the anterior wall.

Tenth: During the highest point of an erection, micturition can be accomplished, although not with the same force as otherwise, but this fact proves conclusively that the urethra is not occluded. This point has been noted in the insane and I have personally observed it in cases.

Eleventh: It may be argued that the prostatic muscle contracts, narrowing the urethra, and thus aiding in the occlusion of the canal. This cannot occur to a material degree, for the muscular arrangement is not such to permit it.

According to Walker the function of the verumontanum is to afford a prominent eminence or hill on which the ejaculatory ducts empty. It is a well known fact that in the testes and epididymes, the vast majority of the spermatozoa have little or no motion and it is believed that the addition of prostatic secretion fluidifies the semen and promotes motility of the spermatozoa. The mixture of thick gelatinous semen with the thin prostatic secretion must occur at the moment of ejaculation and must be perfectly homogeneous, otherwise large numbers of the organisms remain in the thick gelatinous portion of the fluid. This necessitates some anatomical arrangement which is afforded by the ejaculatory ducts emptying on the prominence of the verumontanum. The prostatic ducts open on the floor of the urethra, thirty or forty in number on either side of the urethra. The ejaculatory ducts open in the crest of the verumontanum. Walker has found by serial section and by sticking fine objects into the mouths of the ducts that all the ducts converge toward the verumontanum and are directed so as to eject their secretion toward the openings of the ejaculatory ducts. It now becomes evident, according to him, why we have a projection here in the form of the verumontanum, namely, to be in a position so that the thirty to forty prostatic streams issuing simultaneously from the floor, sides and roof posterior and anterior can reach the ejection from the ejaculatory ducts.

Physiology of the sinus pocularis. The exact function of the sinus pocularis is not known. That it is more than an embryonic rest is evidenced by the activity of its epithelium and the marked development of the muscle walls surrounding its glandular content. It secrets a thin alkaline secretion which probably acts as an adjuvant to the prostatic secretion in fluidifying the semen. According to Walker, after castration, in the hog, the cells atrophy and the muscle and elastic fibers almost disappear. He therefore believes that it furnishes a secretion which is necessary for the semen. However, its excision in no way interferes with the fecundity of the semen as observed by the author.

The ejaculatory ducts. The ejaculatory ducts course obliquely through the prostate, pierce the urethra, ascend into the verumontanum and open on its surface in a manner already described.

They are separated from the prostate and sinus pocularis by their own particular thick investment, which is composed of fibrous tissue with a generous admixture of muscle fibers. The portion of the ejactulatory ducts in the verumontanum and the sinus pocularis have a common investment or tunic and the ejaculatory ducts are further separated from the sinus pocularis by their own particular tunic. Porosz claims that the ejaculatory ducts make a bend in the verumontanum somewhat like a hook and that in this portion it has an increased muscular investment which gives to it sphincteric action. This muscle he calls the "sphincter spermaticus." Upon the tonic or atonic condition of this muscle depends, according to him, the physiological and pathological explanation of many of the sexual phenomena. The greater the tone of the sphincter spermaticus, the greater the number of aggregate stimuli are necessary before an emptying of the seminal vesicle contents takes place. If the sphincter spermaticus is atonic, on the other hand, very little stimulus is necessary to cause relaxation. From this tonic and atonic behavior of the sphincter he explains the different degrees of pleasurable sensation accompanying the sexual act, e.g., prococious ejaculation, retarded ejaculation, spermatorrhoea, etc. Felix, who has made a careful study of the anatomy of the ejaculatory duct, denies that the duct has an internal circular arrangement of muscle fibers together with an external arrangement running lengthwise. According to him the circular muscle fibers form a complete ring only in the region of the seminal vesicles and the nearer we approach the verumontanum portion of the duct, the more indefinite does its muscular tunic become. In my investigations, I did not observe anything which would lead me to accept Porosz's theory. Furthermore, if this theory were correct, sexual disturbances would result following the excision of the verumontanum, with its contained sphincter spermaticus, symptoms which I have never observed following the radical removal of the colliculus.

Of little interest has been the question of the possibility of the ejaculatory ducts ever emptying into the sinus pocularis, some claiming it occurred, others denying the possibility. Porosz in serial sections in three hundred cases and Lowsley in three hundred and fifty cases examined serially, never observed it once. Mihalkovics, Henle and others have claimed that it may occur. That it can occur is evidenced by the accompanying photograph (fig. 7). Full serial study of this specimen shows a bold entrance of one ejaculatory duct into the sinus pocularis. This specimen is also unique in that the gland acini of the sinus pocularis do not open by smaller and larger ducts into the grand or common duct, but they empty into a number of ducts, which open independently on the surface of the verumontanum. Furthermore, there is no evidence whatever of a common duct present in this specimen.

In one case the sinus pocularis instead of being composed of glandular acini emptying by ducts into the common duct, seemed to be composed of long narrow duct-like tubules whose termination did not suggest acini, but which opened however, into the common duct (fig. 5).

SUMMARY

The verumontanum is an elevation formed by the upward projection of the sinus pocularis carrying before it the mucous membrane of the posterior urethra.

The verumontanum is made up almost entirely of the sinus pocularis together with the ejaculatory ducts and occasionally a few prostatic ducts.

It is not a cavernous structure, indeed the blood supply is not any greater than the surrounding tissue, therefore, its function cannot be of an erectile kind.

Excision of the verumontanum does not interfere with the physiology of copulation or the fecundity of the semen.

It has been demonstrated that the ejaculatory duct may open into the sinus pocularis.

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PLATE 1

FIG. 1. Cross-section through the center of the verumontanum. *A*, Surface mucous membrane; *B*, pit formation; *C*, common duct opening on surface of verumontanum; *D*, gland acini; *E*, tributary duct; *F*, wall or capsule of sinus pocularis.

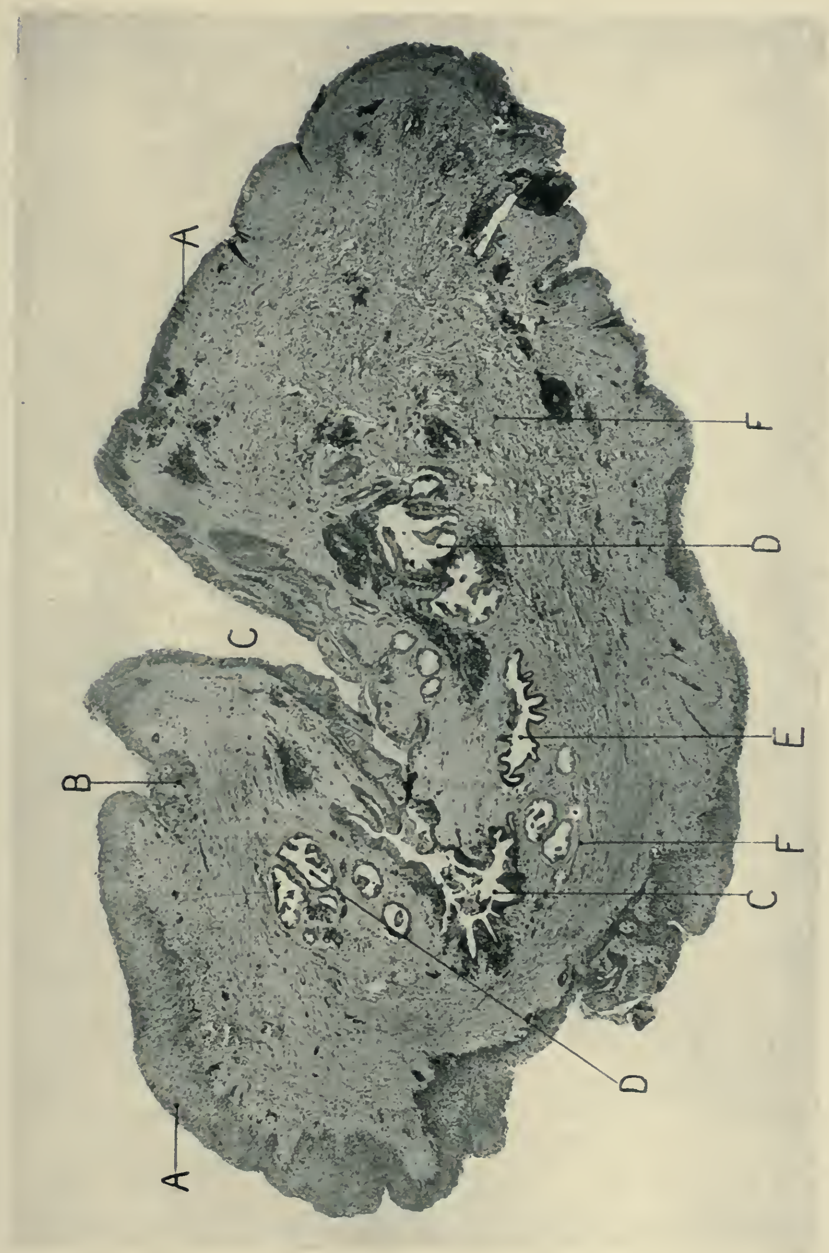
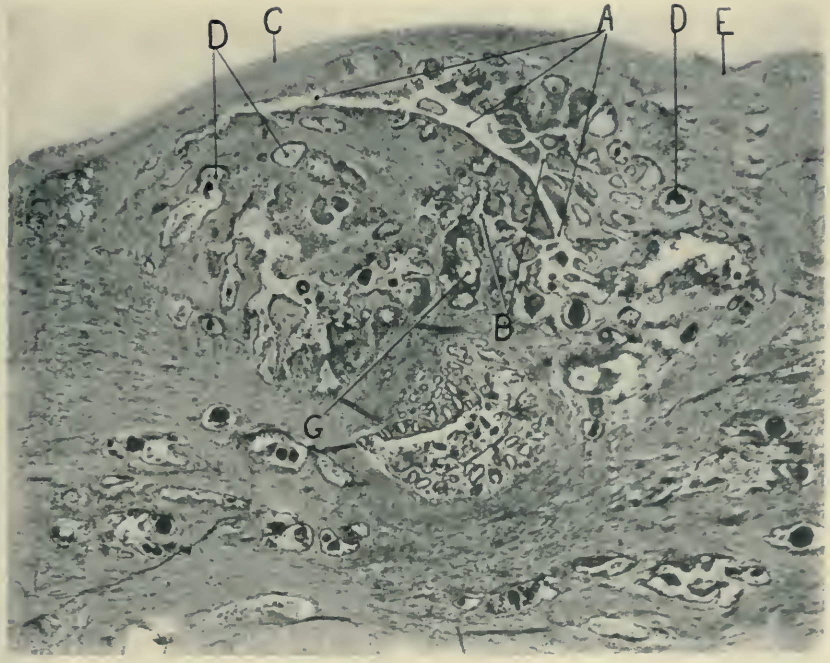

A
A
B
C
C
D
D
E
F
F

PLATE 2

Fig. 2. Long section through center of verumontanum. *A*, Common or grand duct, coursing obliquely through the sinus pocularis, receiving as tributaries the smaller ducts *B*. It terminates a short distance below the surface of the verumontanum *C*. *B*, smaller ducts emptying into common ducts; *D*, sinus pocularis acini; *E*, the mucous membrane is here present, elsewhere it is detached; *C*, surface of the verumontanum. Note what a small amount of tissue remains of the verumontanum proper, if you exclude the sinus pocularis with its contained wall. *F*, Wall of sinus pocularis, its continuation from the prostate and its insensible blending with the urethra can be traced; *G*, ejaculatory ducts.

Extension of Line *G*, upward erroneous, should have been extended downward to include acini like invaginations below.


D
C
A
D
E
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G

PLATE 3

Fig. 3. Few later sections showing the sinus pocularis opening on the surface. In this specimen there is no common duct. *A*, Opening of sinus pocularis on surface of verumontanum; *B*, ejaculatory duct. Note the similarity between the ejaculatory duct and the sinus pocularis acini. *C*, Prostatic ducts; *D*, sinus pocularis acini.

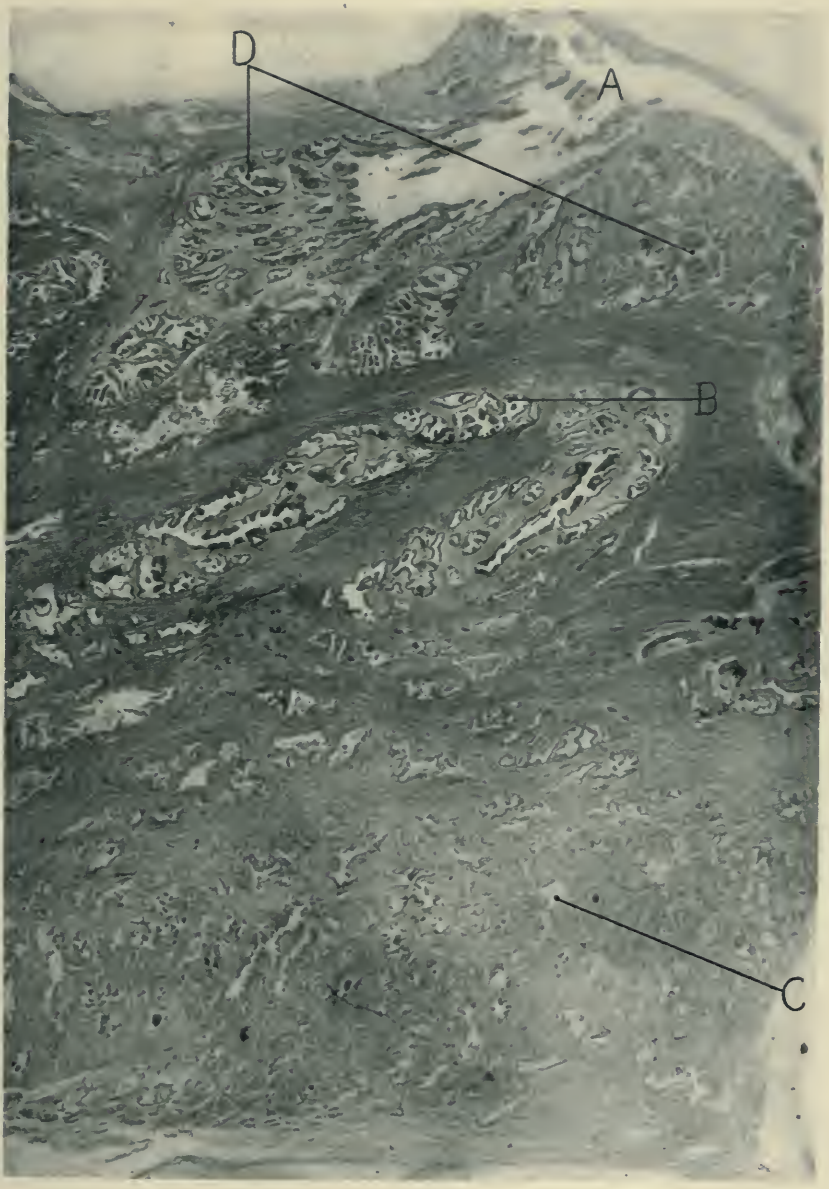
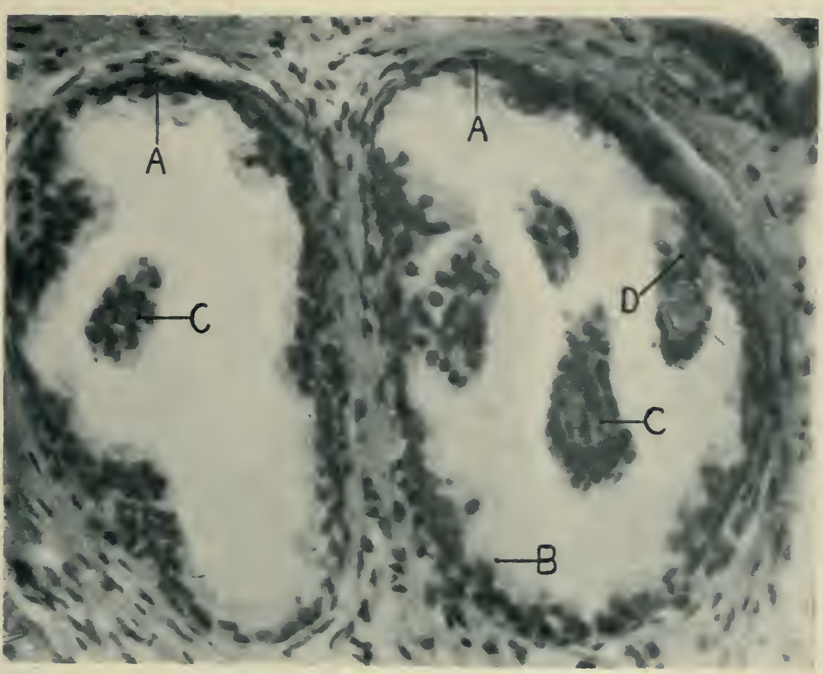

D
A
B
C

PLATE 4

Fig. 4. Two sinus pocularis acini. Showing their finer histology, namely, wall or basement membrane of connective tissue on which are immediately apposed two or three layers of simple cuboidal epithelium. *A*, Wall of acini; *B*, cuboidal epithelial cells; *C*, invagination process of epithelial cells broken loose from the wall of the acini; *D*, invagination process not detached from wall.

Fig. 5. Section showing cystic dilation of a sinus pocularis acinus. *A*, Acinus with cystic dilation; *B*, normal acini; *C*, ducts.



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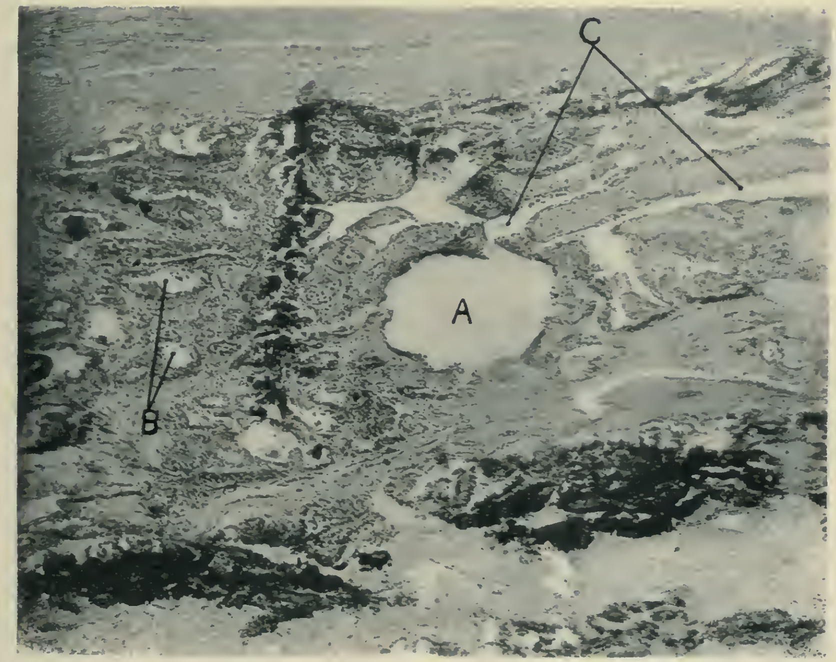


5

PLATE 5

Fig. 5A. Cross section through the sinus pocularis. Showing the duct-like bodies without acinous formation (see text). *A*, Duct-like bodies sectioned lengthwise; *B*, cross-section of duct-like bodies.

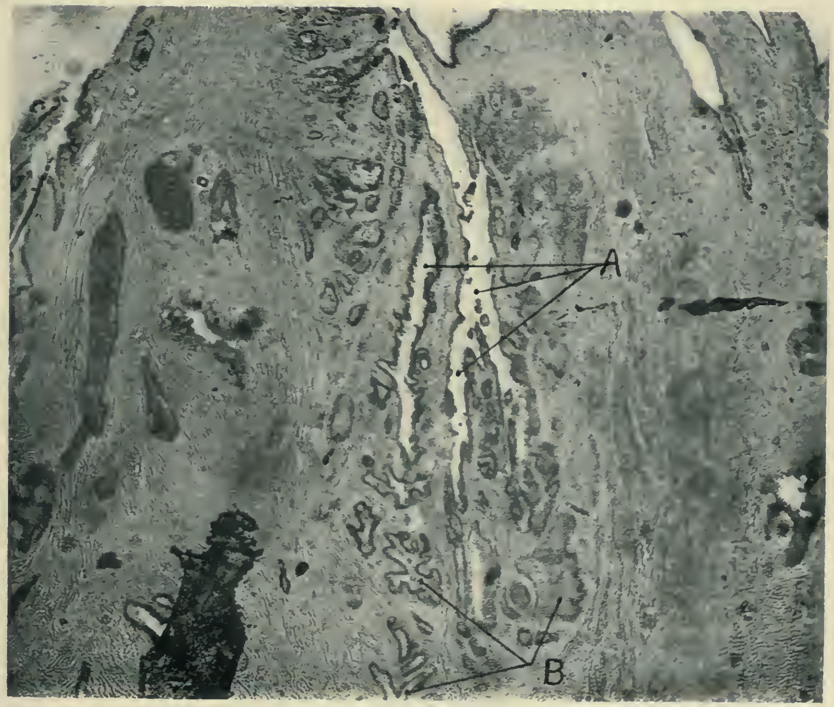

A
B

PLATE 6

Fig. 6. Long section through center of sinus pocularis. *A*, Common duct opening on surface of verumontanum; *B*, acini, some simple, some showing invagination processes; *C*, wall of acinus which can be traced like in section above; *D*, ejaculatory duct.

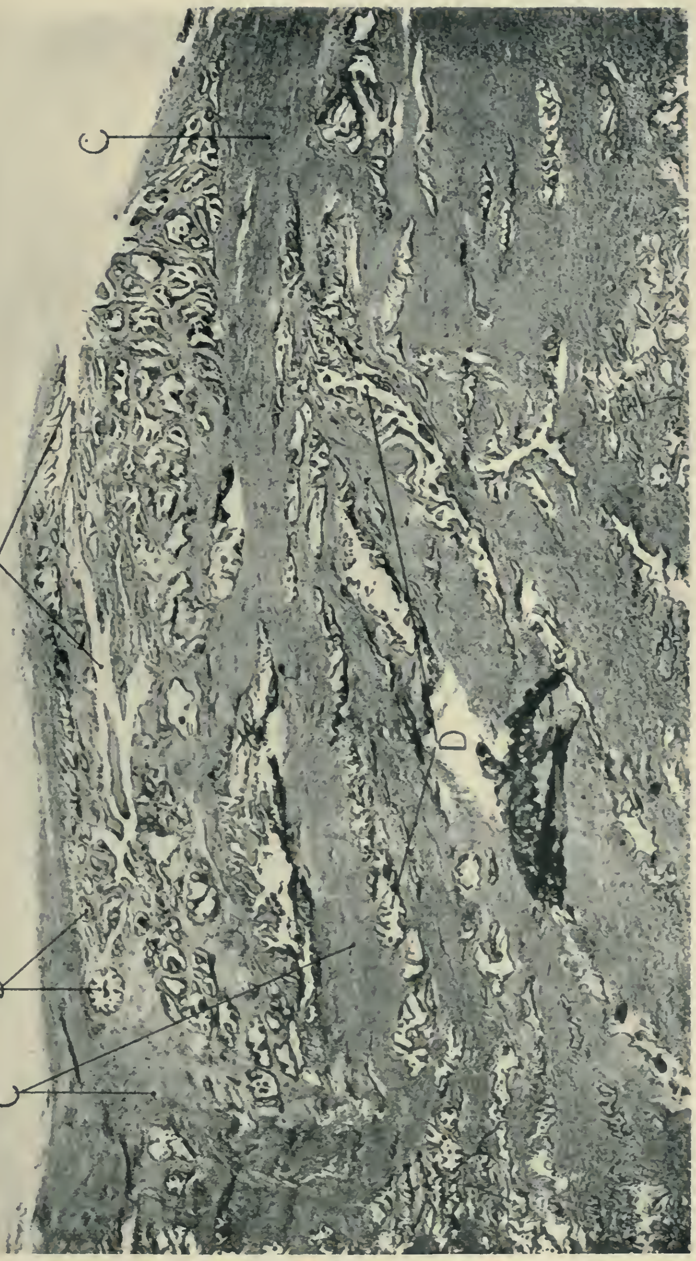
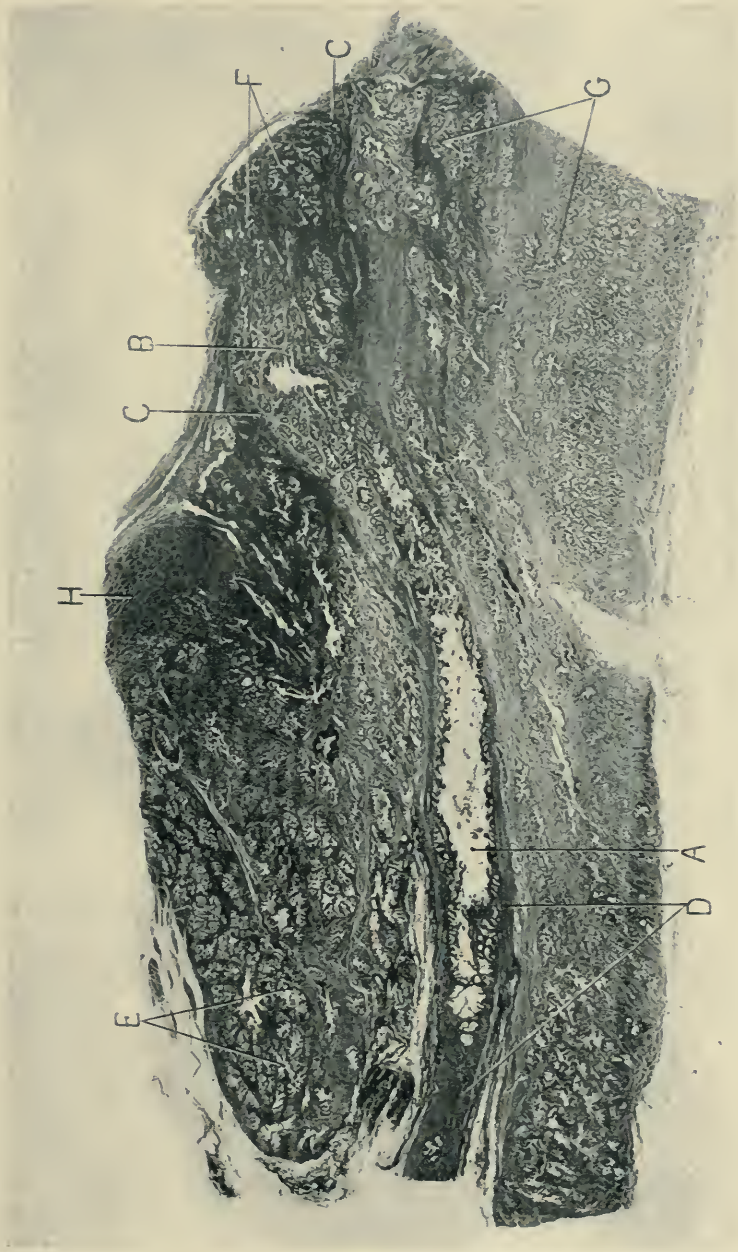

C
A
D
B
C

PLATE 7

FIG. 7. Long section showing ejaculatory duct coursing through the prostrate and emptying boldly into the sinus pocularis. *A*, Ejaculatory duct; *B*, sinus pocularis; *C*, wall of sinus pocularis; *D*, wall of ejaculatory duct; *E*, prostatic acini. Note the similarity between them and the sinus pocularis acini. *F*, Sinus pocularis acini; *G*, prostatic ducts; *H*, vesical sphincter muscle. In this section the sinus pocularis did not yet open on the surface.



C
F
G
B
C
H
A
D
E

PLATE 8

Fig. 8. Sinus pocularis acini filled with corpora amylacea. *A*, Corpora amylacea.

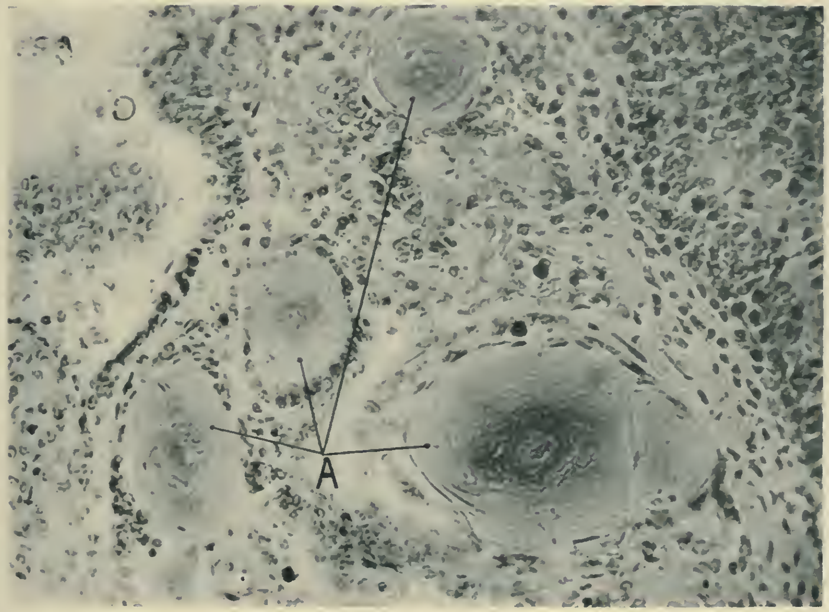
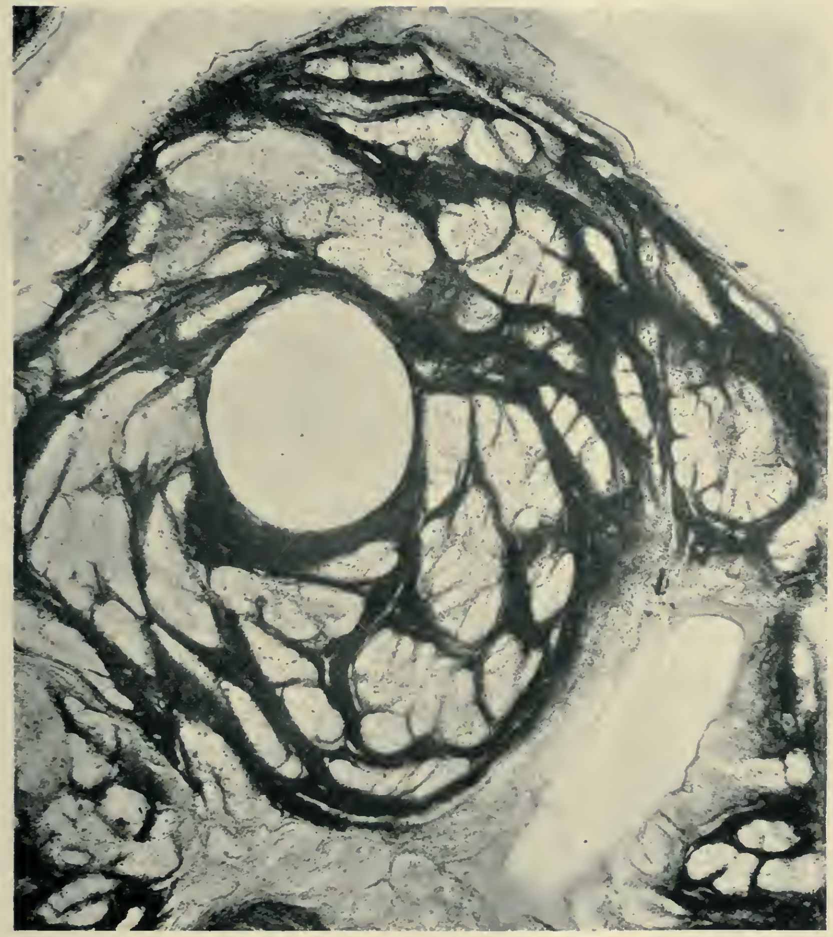

A

PLATE 9

Fig. 9. Section of verumontanum. Showing elastic tissue formation. Photograph includes glandular portion of sinus pocularis. Darkened areas represent elastic tissue. Note how it enters into the formation of the acini and the stalks of the infolding processes.



THE RATIO BETWEEN THE UREA CONTENT OF THE URINE AND OF THE BLOOD AFTER THE ADMINISTRATION OF LARGE QUANTITIES OF UREA.

AN APPROXIMATE INDEX OF THE QUANTITY OF ACTIVELY FUNCTIONING KIDNEY TISSUE.

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The procedures which are at present regarded as the most accurate means to use in determining the function of the kidney have their origin in two fundamentally divergent views as to the mode of action of the normal kidney. Schlayer emphasizes the essential inconstancy in the rate of work of the kidney even under uniform conditions, while Ambard believes that variations in the rate of excretion of urinary constituents under any and all conditions are in reality manifestations of the constancy of kidney action, since they are exactly accounted for by alterations in the concentration of these constituents in the blood and in the urine, and do not result from inconstancy in the rate of work of the kidney itself.

The practical significance of these views is illustrated in the methods which have grown from them. Schlayer (1), believing that at any given time the kidney may be working either quickly or slowly in accordance with an unpredictable factor which he terms the "Reizzustand," draws the logical conclusion that no inferences as to the total functional capacity of the kidney can safely be drawn from observation of the rate of excretion of urinary constituents. The same kidney under the same conditions may at one time excrete much and at another time little. All that can be said is that in the one case it is in a state of hyperexcitation and that in the other the excitability is depressed. It naturally follows that all attempts to draw quantitative anatomical inferences from functional findings are illusory, and should be abandoned. It is true he finds that certain interrelationships between the rates of excretion of sodium chloride and water are characteristic of changes beyond the normal range of variation in the relative excitability of the "vascular" and tubular parts of the kidney, and that where the "vascular" apparatus is involved there is a decrease in the rate of excretion of lactose, and a decrease in KI excretion when the tubules are deficient, but he expressly states that at most only qualitative deductions can be drawn as to the presence or preponderance of one or the other type of lesion. It is not possible from such functional studies to determine how much of the kidney has been involved or destroyed by disease.

Ambard (2) on the other hand, holding that normally there is no variation in the rate of excretion apart from changes in the concentration existing on either side of the kidney cells, states that any departure from the rate of excretion which should according to his formula result from these determinable concentrations, is indicative of functional disorder. Although he does not draw exact quantitative anatomical inferences from the degree of change in his coefficient, there is no logical reason why this should not be done if the premises on which the formula is based are sound.

These views are so important and yet so divergent that some years ago we started a reinvestigation of the mode of action of the normal kidney.

Schlayer was considerably embarrassed in his work by the fact that the test-substances he chose—chlorides and water—are markedly subject to extra-renal influences. He admits that part of the variability in his twenty-four-hour rates of excretion may arise not from any difference in the excitability of the kidney cells, but from inequalities in the amounts of chlorides and water brought to these cells for excretion. As a matter of fact, we have knowledge of extra-renal factors which make it seem improbable that any considerable degree of uniformity in the rate of delivery of chlorides and water to the kidney is likely to be achieved even though the intake in the diet is constant. For neither chlorides nor water can be regarded as simply waste products which the economy of the body strives only to rid itself of. They both play an important part in physical and chemical metabolism and in particular are subject to regulation by the mechanism whereby osmotic equilibrium is maintained in the body. Furthermore, both of them have other sources of excretion; water through the lungs, intestines and skin; and chlorides into the stomach. And it must be remembered that though the ultimate discharge of water and chlorides from the gastro-intestinal tract is relatively small and uniform, the temporary excretions into the stomach and intestine are very large and not susceptible of measurement. Thus, though only 100 or 200 cc. of water are found in the stools it has been calculated that the volume excreted into the alimentary tract with secretion from the stomach, liver, pancreas, and intestine at various times during a twenty-four-hour period approximates 4000 cc. The total quantity of chlorides secreted into the stomach is also large, and the rate of secretion is variable at different periods throughout the twenty-four hours.

The objections we have mentioned to the use of water or of chlorides for the purpose of measuring the variability of kidney action do not apply to some other urinary constituents, such as uric acid or amino-acids, but on the other hand they have disadvantages of their own, for they are not true end-products. There is still a question as to whether uric acid may not in part be decomposed within the body and amino-acids may be retained for synthesis or may be deamidized.

The ideal test-substance would be a urinary constituent which was a true end-product in that it was incapable of chemical alteration within the body, one which subserved no physical function, so that its concentration in the blood would not be limited by any of its physical properties, and one whose only path of excretion was through the kidneys. Finally it should be possible at will to produce marked and uniform increases in the concentration of this substance in the blood supplied to the kidneys.

To a quite remarkable degree, urea fulfills these requirements.

There is no agency within the tissues which can either break it down or use if for synthesis.[1] It is present in all the tissues in concentrations which are substantially the same and which seem to depend only on the amount of urea solvents they contain (7).

Another very important property of urea from the point of view of its use as a substance for testing the work of the kidney, is the possibility of producing very marked increases in the urea concentration of the blood and tissues without disturbing any essential physical equilibrium of the body. Thus we have frequently induced in healthy individuals concentrations five or six times greater than the normal, a degree of increase which would be impossible with water or chlorides because of the disturbance of the osmotic balance which such concentrations would entail. Urea apparently does not give rise to any appreciable degree of osmotic pressure, because there are no barriers to its free diffusion through the whole organism. When urea enters the stomach, it begins to pass as once through the stomach wall and in a remarkably short time has become evenly distributed through all the tissues in accordance with their water content. This equality of concentration is confined not only to the tissues, but also to their secretions. The bile (7), and the milk (8), have a urea concentration similar to that of the blood. No observations, so far as we know, have yet been made on the urea content of the secretions of the stomcah or pancreas, but we have not any reason to believe that they are exceptions. Herter (9) has shown that during the intravenous injection of urea in dogs, no urea enters the intestine until the blood concentration of urea has risen to about 0.2 per cent. Even then the concentration of urea found in the intestinal contents does not exceed 0.1 per cent and is usually much less. We therefore have some direct as well as indirect evidence that the kidney is the only path by which any active excretion of urea takes place.

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[1] Grafe (3) believes that during protein starvation administered urea may be used to a small extent within the body, but the work of Henriques and Andersen (4) has shown that these results may be ascribed to the retention of nitrogen of bacterial origin from the intestines, or to simple retention of unaltered urea. Abderhalden (5) has confirmed this and has further demonstrated that the administration of large quantities of urea has no effect on protein metabolism. Barnett and Addis (6) found an increase in the ammonia content of the blood after intravenous injection of large quantities of urea in rabbits in whom the circulation of blood through the alimentary tract had been occluded. These results are however susceptible of interpretation otherwise than by the splitting of urea within the body.

Urea has a still further advantage over other substances which have been used to test the functional capacity of the kidneys, in the fact that we know exactly what part of the kidney is directly involved in concentrating the urea from the blood. Leschke's (10) micro-chemical studies, which have been confirmed by Oliver (11), leave no room for doubt that it is only within the cells of the proximal convoluted tubules that this concentration occurs.

There is thus a divergence in the physiological functions and physical properties of water and chlorides on the one hand and in urea on the other. Water plays a part in most of the chemical reactions occurring in the body, while urea once formed is chemically indifferent. Both water and chlorides are held within narrow limits of concentration by the mechanism which maintains a constant osmotic pressure, while urea can vary in concentration to an extent which is determined only by the balance between the rate of entry of urea into the body and the rate of its elimination from the body by the kidneys. Water and chlorides have other channels of temporary or permanent excretion than the kidneys, while urea is actively excreted by this path only.

These properties, or rather want of properties, of urea as opposed to other urinary constituents, are all such as to make it easier to attain that relative uniformity in rate of delivery to the kidney which is essential if its twenty-four-hour rate of excretion is to be used as a measure of the variability of kidney function.

Many of these special advantages of urea have been known for a long time, but they have not been taken advantage of because of the complexity of the methods required for the accurate determination of urea in the urine and blood. Neither the hypobromite method of urea estimation, nor the indirect method of total nitrogen estimations, can give sufficiently accurate results for the determination of the degree of variation in the rate of excretion of urea. It was not until the appearance of Marshall's application of the urease method to urea determinations in urine and blood, that it was feasible to carry out the large number of estimations which are necessary in order satisfactorily to determine such a question.

The quantities of urea excreted by a series of normal individuals on the same diet are not indentical. The differences presumably arise because in some protein catabolism exceeds anabolism, so that most of the amino-acids derived from the disintegration of food and tissue protein are deaminized with the consequent formation of relatively greater amounts of urea, while in others a greater proportion of these amino-acids are used in synthesis, so that smaller amounts of urea are formed. The variations in the rate of urea excretion arising from this cause were eliminated by dividing the experiments into two periods, a fore-period in which the average amount of urea formed from the constant quantity of protein in the diet and from the tissues of each subject was determined, and an experimental period in which 20 or 40 grams of urea were ingested at the commencement of each day. The urea excreted during the foreperiod subtracted from the urea excreted after urea had been taken gave the rate at which the administered urea was eliminated.

This statement would be correct only if the amount of urea derived from food and tissue protein remained the same in each individual during both the fore-period and the experimental period. Any such assumption would be unwarranted. We know that there are not only differences in the level of protein catabolism in different individuals, there are also variations in the metabolism of the same individual from day to day. The differences in the rates of excretion of administered urea might then be due in part or altogether not to variations in kidney activity but to changes in individual metabolism. This cause of variation in rate of excretion was eliminated by comparing the degree of variability in two groups of individuals, one of whom took no urea and the other 20 or 40 grams of urea. The urea of the fore-period was subtracted from the urea of the experimental period, and the average deviation from the mean was determined for each group. If the variability thus measured should be as great in those who took no urea as in those who took urea, it is evident that the variability may be ascribed to the same cause in both groups—variation in metabolism in the same individual, from day to day—and that we could say that a high degree of uniformity in the rate of excretion of the administered urea must have been present since any differences which may actually have occurred, were not sufficient to increase appreciably the variability of the urea group. The average deviations for the average twenty-four hours of the experimental period were 1.41 grams urea in those who took no urea, 1.40 grams in those who took 20 grams of urea, and 1.43 grams in those who took 40 grams of urea. We therefore concluded that under these conditions there was no evidence of any inconstancy in the rate of work of the kidney. The reaction of the kidney to a constant stimulus is constant. Normal renal function measured over periods of twenty-four hours is not characterized by the intrinsic tendency towards variation described by Schlayer, but is uniform under uniform conditions (12).

This conclusion is identical with that at which Ambard arrived except that his observations extended over periods of about one hour instead of twenty-four. He excluded one important extrarenal cause of variation in rate of excretion—changes in the amount of the substance to be excreted brought to the kidney—by determining the concentration of this substance in the blood during the period over which the rate of excretion was measured. In the case of urea he found in individuals who happened to have the same concentration of urea in their urines, that the rates of excretion were proportional to the square of the bood urea concentrations, while in those in whom the blood concentrations were the same, the rates were inversely proportional to the square root of the concentration of urea in the urines. Uniting these mathematical expressions in one formula, he obtained a constant from which the rate of urea excretion could be predicted in any normal individual from the concentration of urea found in his blood and urine.

The laws of urea excretion on which Ambard's formula is based can only be verified after a considerable series of observations have been collected. For from this series only those instances can be taken in which either the blood or urine concentrations are alike. On reviewing our data, which had been collected over several years, we found 271 instances to which one or other of the two laws were applicable. Neither of them were verified, on the contrary there was very positive evidence not only that they were incorrect, but also that no mathematical formula could be constructed which would allow of even a rough prediction of the rate of urea excretion to be expected from any observed concentration of urea in the blood or urine (13). In the formulation of these laws, Ambard was undoubtedly misled by a chance agreement of the few observations on which he depended.

Although it was thus shown that the hourly rate of urea excretion by the normal kidney was not governed only by the urea concentration of the fluids on either side of the urea secreting cells, there remained the question of the degree to which it was influenced by these factors.

In order to determine the effect of changes in blood urea concentration, all the observations were plotted on a scale in which the abscissa represented blood urea concentrations and the ordinate hourly rates of urea excretion. It was found (14) that a curve could be drawn through these points which indicated that the blood urea concentration had a marked effect on the rate of urea excretion. When there was 20 mgm. urea per 100 cc. of bood the average hourly rate was 0.4 grams, with 40 mgm. 1.1 grams, with 80 mgm. 3.2 grams and with 120 mgm. 5.3 grams. But the observations showed a very considerable degree of scattering above and below this curve, so that at any given blood concentration there were wide differences in the recorded rates. For instance at a concentration of 40 mgm.

of urea per 100 cc. of blood the chart records rates ranging from 0.6 to 2.29 grams of urea per hour. It is evident therefore that the effect of changes in bood urea concentration only becomes clearly apparent when an average of a number of instances are taken. In any individual case the effect may be counterbalanced by other factors.

The conception that these variations in the rate of urea excretion occurring even when the blood urea concentration is constant, may be due to differences in the urea concentration of the urine, is one which from a purely theoretical point of view has much in its favor. For if the concentration of urea in the blood on one side of the kidney cell has, as we have shown, a pronounced effect on the rate, it sees likely that the concentration of urea on the other side of the cell, that is in the urine within the lumen of the tubules, should also have some effect. It might be expected that the diffusion of urea from the cell to the urine would be retarded when the urine concentration was high, and hastened when it was low. But this hypothesis is not supported by the facts (15). The rate of urea excretion is independent of the concentration of urea in the urine, and there is no evidence at all that any direct relation exists between them. If there had been, we should have been able to detect a general tendency towards high urine concentration in those cases in which the rate of excretion was less than the average found at any given blood concentration, and that a low concentration generally accompanied an unusually rapid rate of excretion. No such general tendency however was demonstrable. This after all is only what might have been expected if a broad view is taken of the function of the kidney in relation to the needs of the organism as a whole. For if the rate of excretion of urinary constituents were to rise and fall in accordance with the volume of water available for excretion, we should even under ordinary conditions of life be subject to a variation in kidney action which bore no necessary relation to the metabolic requirements of the body. It is not to be wondered at that kidney activity is not subject to the physical laws of diffusion or osmosis nor even in all probability of surface tension or adsorption. The phenomena of life are characterized by a continual annulment and overruling of the physical laws which inert material obeys. The increase in the rate of excretion of urea which accompanies an increase in blood urea concentration, although it is in general what might be expected on physical grounds, yet in detail cannot be even approximately so explained, while in the absence of a relation between the rate of excretion and concentration in the urine, we have an example of the manifestation of a force which acts in direct opposition to physical laws. Of the nature of this force we of course know nothing. All that we can say is that it acts for the good of the organism as a whole. It prevents any marked accumulation of urea in the body by increasing its rate of work when the blood urea concentration rises, and it does not allow variation in water excretion to interfere with this work.

Though we may speak of a regulation of the urea content of the tissues and of the blood by the kidneys, there is no such close regulation as is maintained in regard to other substances such as for instance the H ion concentration or even the concentration of chlorides. We found variations of from 24 to 60 mgm. of urea per 100 cc. in the blood of normal individuals even though the blood was taken in the morning before food (16). One individual on whom 50 estimations were made under these conditions showed variations of from 25 to 60 mgm. In a group of 28 subjects on a constant diet the blood urea content taken on the third day of the diet varied from 16 to 44 mgm. These changes were noted in subjects who had taken no urea.

It would seem then that within these limits the urea content of the blood is a matter of comparative indifference to the body. This no doubt arises from the fact that urea subserves no function and is foreign to the body. We have evidence that these variations in blood urea concentration parallel changes in the rate of protein catabolism, rising and falling with them. But this is certainly not their only cause. They may also result from changes in the activity of the kidney. During sleep the kidney is less active as regards urea excretion and the blood concentration tends to rise. There are also states of kidney inactivity which may be induced by the absence of food and water. These variations in activity are of course not intrinsic in origin, but arise from the action of other factors than the urea concentration of the blood. The marked effect of these other factors is illustrated in the wide variation in the rates of urea excretion which were noted in the same individual when the blood urea concentration was constant.

The facts determined by this study were, then, that the rate of urea excretion was independent of the concentration of urea in the urine, and that a relation existed between the rate of urea excretion and the blood urea concentration. This however was only a general relationship within which a wide variability was found. It should be stated that this variability was not confined to experiments in which the conditions as regards food and water intake, time of day, etc. were different. We found a marked variability in those subjects who were on a constant diet, and in whom there was no demonstrable inconstancy in the twenty-four hour's rate at which they excreted administered urea. The same kidneys were at the same time both variable and constant in their mode of work.

This apparent contradiction arises from the difference in the length of time of the periods during which the rate of excretion was measured. Over twenty-four-hour periods the output of the kidney is found to be constant. But when the output for each hour of the twenty-four is measured, considerable variability is found. There are retarding and accelerating factors which alter the rate over short time periods, but leave it unaffected over longer periods because they counterbalance one another. If during one hour the rate is unusually slow, it will be more than ordinarily rapid during a later hour, so that the total twenty-four hours excretion will remain the same. The variation in the hourly rate of excretion in individuals who have the same blood urea concentration are due to the action of these temporary and balancing phases of excitation and of depression in kidney acitvity.

These observations have a direct bearing on the question of what methods are best adapted to measure the functional capacity of the kidney. The failure to find any variability in the twenty-four-hours rate of excretion of administered urea in individuals free from kidney disease is significant since it raises the hope that variation from the normal rate of excretion may be a measure of the degree of functional and anatomical abnormality. But the conditions under which this normal constancy of function were observed are of still greater significance. It was seen in connection with the twenty-four hour rate of excretion of a substance which is essentially foreign to the body. It was observed in subjects who had all taken the same amounts of protein, salts and water. It was obtained under conditions involving an unusual strain on the capacity of the kidneys. Reasons for the special importance of the last point will be given later in the paper, but it may be said now that under such conditions, where the kidney is wakened to full activity under the influence of strain,[2] and where dietary factors are the same, the blood urea concentration tends to be constant except for such variations as arise from differences in protein metabolism. The effect of these variations on the amounts of urea excreted are measured during the fore period and in the main excluded by subtracting the average of the fore-period from the urea excreted in the experimental period. In effect therefore the result may be regarded as a measurement of the ratio between the urea content of the urine and of the blood, under conditions in which the blood concentration remains the same.

We have data on the mode of reaction of individuals suffering from disease of the kidneys under the above conditions, which we hope later to report in detail. There is one observation in this connection which may be cited now, since it illustrates a fact which is applicable to all methods of testing kidney function. We cannot by any strain within the bounds of practicability attain to a measure of the absolute maximum of the rate of excretion of any urinary constituent. All we can do is to determine the maximum rate in relation to a given concentration of the substance in question in the blood. If the concentration in the blood is increased still further, the rate of excretion will also increase, until the highest concentration compatible with life is attained. This was demonstrated by Herter when he showed that the rate of urea excretion in dogs increased up to the point where the animals died in convulsions because of the enormous quantities of urea injected. But it is not so evident that this would be the case in diseased kidneys. We might suppose that damaged kidneys would grow tired so that they would not longer respond by increased work to an increased load. But our experience shows that what is true of normal kidneys is true also of those which are diseased. As an example we may cite a case of subacute diffuse glomerular nephritis. The average normal twenty-four hours rate of excretion of administered urea following three doses of 20 grams given on consecutive days is 16.6, 18.7, and 18.9 grams. This patient however excreted only 6 grams after the first dose of urea thus retaining 14 grams, so that when 20 grams was taken again at the beginning of the second day, his kidneys were called on to excrete 34 grams. He responded to the call for increased work and eliminated 14.9 grams. On the third day his rate of excretion rose still higher to 18.9 grams. Thus the apparently paradoxical circumstance may be met with in which a patient with severely damaged kidneys is excreting greater quantities of urea than is an normal individual. The characteristic of the diseased kidney is not its incapacity to excrete large amounts of urea, but its incapacity to excrete as much urea as the normal kidney does in relation to the urea content of the blood. The diseased kidney will only excrete as much urea as the normal after it has failed to eliminate the urea as quickly as the normal, and has thus increased the amount of work which it is called on to perform through its own incapacity. In the particular test we are discussing, the essential point is the time which the kidney takes to respond to the extra load thrown on it by the ingested urea. A low rate of excretion during the first few hours after urea administration is the special characteristic of decreased functional capacity.

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[2] The more work the kidney is called on to perform, the less subject does it become to temporary fluctuations in rate of work. It should be noted, and this is a point we did not appreciate at the time the work was done, that this fact makes it impossible to conclude that any absolute constancy in the rate of excretion of administered urea was present in our experiments. For the urea group were under strain and might be expected to show somewhat less variability than the non-urea group. There may therefore have been some variability in the rate of excretion of the added urea, though the figures show that if present it could only have been of slight degree.

Any method of testing functional capacity which involves the necessity for a constancy in diet has only a limited applicability in clinical work. The constant diet however is necessary in order that variations in blood concentration due to differences in rate of protein metabolism may be eliminated. The method used by Ambard of determining the blood concentration during the period over which the rate is measured is a more direct and accurate method of accomplishing this end. But these periods must be short, otherwise the observed blood concentration will not be representative of the average concentration throughout the whole period. And as we have shown when these short periods are taken, we may have marked fluctuations in the rate due to the action of other factors than blood concentration. If however, conditions were found under which these other factors remained constant, the method would be an accurate and simple means of measuring kidney function. This problem resolves itself into a study of those conditions other than blood urea concentration which may influence the rate of urea excretion. The blood concentration has a marked influence, but it is one which can be measured and eliminated. This may be most simply done by dividing the hourly rate by the amount of urea found in 100 cc. of blood.

This ratio is not a mathematical abstraction. It gives the number of times by which the urea in one hour's urine exceeds the urea content of 100 cc. of the blood supplied to the kidney. It expresses the relation between the amount of work accomplished by the kidney and the most important measure of the amount of work the kidney was called on to perform. The question then is what are the factors which may influence this ratio.

On theoretical grounds it might be supposed that the ratio would vary with the amount of blood passing through the kidneys. Two kidneys might be supplied with blood which contained the same amount of urea per 100 cc., but if 20,000 cc. of blood passed through one kidney in the hour and only 10,000 cc. through the other, the total amount of urea which might have been excreted would be twice as great in the one case as in the other, and one ratio might be double the other. We have attempted to estimate the effect on the ratio of changes in the rate or flow of blood through the kidney and though for various reasons we have not succeeded in obtaining generally applicable results, we have evidence which favors the view that variations in the amount of blood passing through the kidney when that amount exceeds a certain minimum, have little effect on the ratio. If the kidney removed all the urea from the blood brought to it, the ratio would of course vary directly with the rate of flow. But we found on comparing the urea content of the renal vein and artery, that the decrease in the vein was only slight (17). We never found a greater difference than 12 mgm. per 100 cc., and in most cases the decrease represented only a small percentage of the urea present. The kidney is supplied with much more urea than it excretes and therefore it does not follow that a further increase in the supply will be followed by any increase in the output. On the other hand circumstances certainly arise in which the rate of blood flow has a very marked effect on the ratio. We have repeatedly noted that any handling of the renal artery is apt to be followed by a visible constriction of the vessel and that at the same time the secretion of urine stops, and the ratio falls to zero. This effect may however be interpreted as indirect. In order to carry out the enormous amount of work entailed in the separation of the urinary constitutents from the blood, a very large supply of oxygen and fuel is required. When this supply becomes defective, secretion automatically ceases. But here again variations in the supply of oxygen so long as it is above a certain minimum, do not appear to have any appreciable effect on the ratio. Thus we have found when the haemoglobin content of the blood is experimentally reduced by repeated haemorrhage, that a definite effect on the ratio is only produced when the degree of reduction is very marked. We think it probable therefore that variations in the amount of blood supplied to the kidneys do not under physiological conditions markedly influence the ratio. Instead of the blood supply ruling the work of the kidney, the evidence rather goes to show that the work of the kidney is largely independent of variations in blood supply. Such variations in kidney blood supply as may passively follow from alterations of the distribution of blood to other parts of the body would therefore be possible without any interference with the work of the kidney. If this view is correct, it is another instance of the comparative freedom of the kidney from passive subjection to mechanical and physical factors.

The differences in the rates of urea excretion which are found to exist in spite of constancy in blood concentration represent of course variations in the ratio we have defined. These variations cannot be explained by the differences in the urine concentration, and there is the evidence we have just given against attributing them to differences in the rate of blood flow through the kidneys. If we had found that certain individuals always gave low and others high ratios, there would be good reason to believe that the variation arose from permanent individual peculiarities, such as might arise from anatomical differences. This however was not the case. In a single individual 110 ratios were determined and a range of variation found which was comparable to that shown by a group of individuals. It would thus appear that the cause of variation cannot lie in differences between the kidneys of different individuals.

Certain facts in regard to the average ratio and to the unexplained variations from the average in the ratio become apparent when each ratio is charted according to the level of the blood urea concentration at which it was observed.

The average ratios represented by the line in figure 1 increase with increase in the blood urea concentration. The more the kidney has to do, the more efficiently does it work. It responds to a call for more work by an increase in output which is greater than the increase in demand.

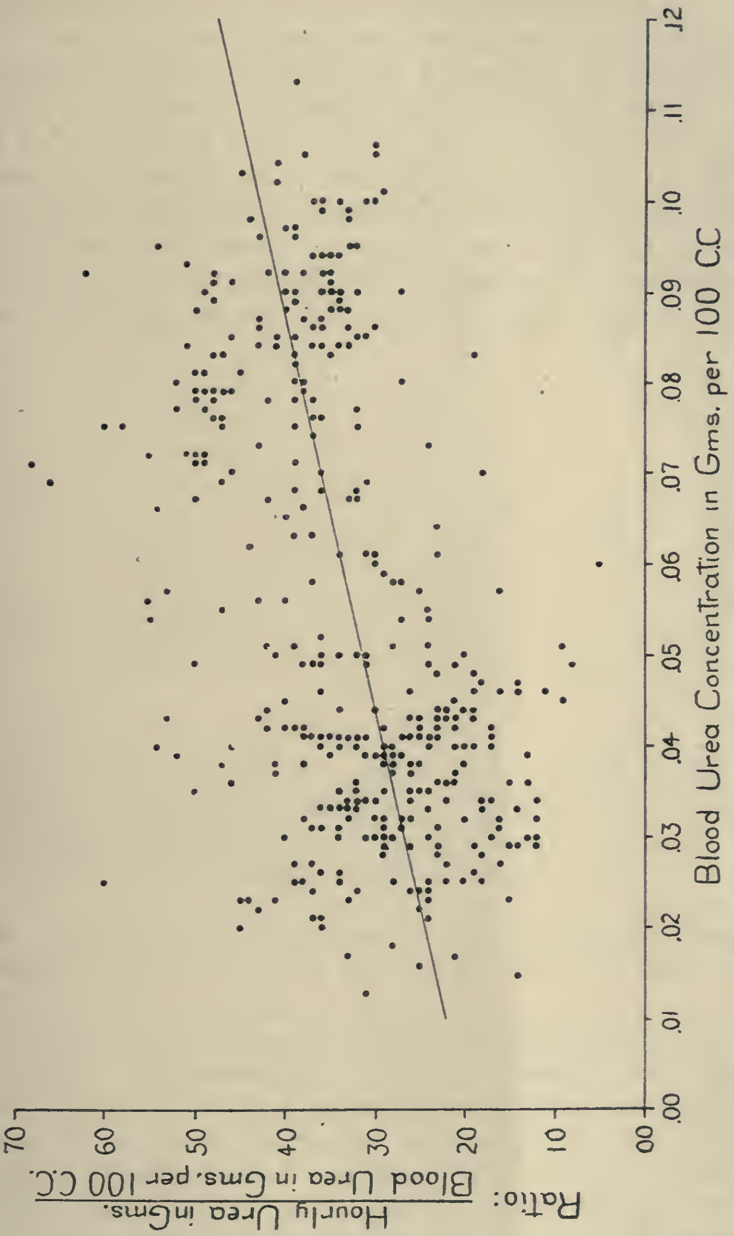

Fig. 1. The Increases in the Ratio with Increase in Blood Urea Concentration.

The variability of the ratio is represented in figure 1 by the scattering of the observations above and below the curve. The variability thus measured is the absolute range of variation. But it is the relative and not this absolute variability which is the true guide to the degree of variation in the activity of the kidney. Thus ratios varying from 10 to 20 have no greater absolute range of variation than ratios of from 50 to 60, but the relative variability is much greater. There is 67 per cent of variation from the average in the first instance, and only 18 per cent in the second. We have therefore determined the median percentage variation from the average ratio as given by the curve in figure 1 at different levels of blood urea concentration (fig. 2).

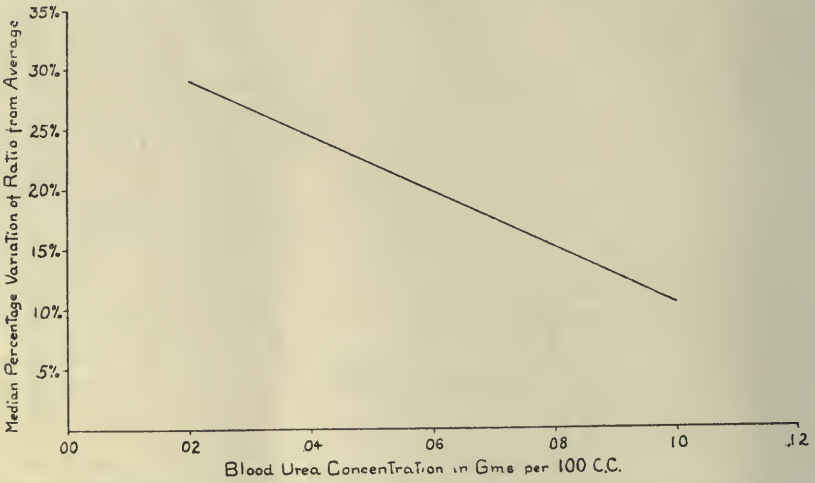

Fig. 2. Decrease in the Variability of the Ratio with Increase in the Blood Urea Concentration

The percentage variability which is represented in figure 2 decreases with increase in blood urea concentration. The more the kidney has to do the more uniformly does it work.

There is then no one average ratio which may be taken as a standard of normal kidney function, but a different average ratio for every blood urea concentration. There is no one normal range of variation, but a series of normal ranges which decrease with rise in the urea content of the blood.

Even at the highest blood concentrations there is a considerable percentage variation which prejudices the value of the ratio over short time intervals as a guide to the functional capacity of the kidneys. If the causes of this variability were known[3] conditions might be found under which it might be lessened. We know that changes in the concentration of urea in the urine and anatomical differences in the kidneys of the subjects of these experiments can be excluded as being to any appreciable extent factors in its production. There is also, as we have shown, reason to believe that variation in the rate of blood flow through the kidney does not under ordinary conditions markedly influence the ratio. There remains the possibility that the ratio may vary with changes in the concentration in the blood of other substances than urea.

There is here a large field for investigation. So far we have only found two substances—adrenalin and pituitrin—which have had a marked and definite influence on the ratio. Adrenalin increases and pituitrin decreases the ratio (18). What we call the normal ratio may possibly simply be that which results from the usual balance in the blood between adrenalin and pituitrin.

This finding has a considerable physiological interest, since it reveals a means whereby the organism frees itself from the bondage which would have resulted from any strict dependance of the rate of excretion on the concentration in the blood of the substance to be excreted. It is another example of the independence of the kidney from the rule of purely physical law, and its regulation by forces working in accordance with the requirements of the body as a whole.

The antagonistic effects of adrenalin and pituitrin may also be of importance in connection with the measurement of kidney function. If the temporary variations in the ratio are due in part to changes in the adrenalin-pituitrin balance in the blood, it will be necessary to find what are the experimental conditions under which the balance tends to be most constant. We have shown that the ratio is most variable when the kidney has little to do. This might be explained by supposing that when there was no accumulation of catabolites in the blood, the balance between adrenalin and pituitrin might fluctuate from one side to the other in accordance with the needs of the body for adrenalin or pituitrin for other than excretory purposes. The result would be a wide variability in kidney action. But when a pressing need arose for the rapid excretion of accumulated end-products the balance would swing only in one direction—towards an increase in adrenalin—and the kidney would become more constant in its rate of work. Again we have shown that the normal kidney meets progressive increases in the amount of work it is called on to perform by augmentations in the rate of excretion, which with every increase in load become progressively greater than that required to simply maintain an equality between work required and work done (fig. 1). This capacity might be attained through a reciprocal relation between the adrenalin content of the blood and the degree of strain on the kidney of such a nature that every increase in strain was met by a still greater increase in adrenalin. Further and more direct data will however be required before such hypotheses can be accepted.

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[3] Part of the variability shown in the great scattering of the observations in figure 1 arises from a constant deviation from the average ratio manifested by the normal kidney at certain time intervals following the ingestion of urea.

The subtitle of this paper expresses the view that the ratio after the administration of urea may be taken as an approximate index to the amount of actively functionating kidney tissue. If this direct relationship exists, the ratio obtained in animals with small kidneys should be proportionately smaller than the ratio in animals with larger kidneys. We have made several hundred observations of the ratio in rabbits, and have found on an average 2.03 times more urea in one hour's urine than was present in 100 cc. of blood when the urea content had been raised to 225 mgm. per 100 cc. At this level of blood urea we should expect from figure 1 a ratio of 66 in man, that is a ratio about 33 times as great. We do not know the relative kidney weights in the rabbit and in man, but these weights will have a relation to their respective body weights. The average weights of our rabbits was about 2 kgm. and an average weight for man is about 70 kgm. or thirty-five times greater than the weight of a rabbit. It would thus appear that the ratio varies in nearly direct proportion to the weight of the kidneys.

Evidence of the above nature only becomes of value when the average of large numbers of observations can be compared. We hope later to be able to extend it by averages for the rat and possibly for the cat also. The insufficient data we have at present tends to support the hypothesis of a direct relation between the magnitude of the ratio and weight of the kidneys.

The question has been more directly approached through only on a very small scale, by the comparison of the ratios following urea administration before and after the removal of one kidney. In three rabbits an average ratio of 1.29 was obtained when both kidneys were functioning, and a ratio of 0.54, or less than half, when only one kidney remained. (19)

It is of course not contended that in individual cases it is possible to demonstrate a constant and absolute relation between the ratio and the kidney weight. There were doubtless differences between the kidney weights of the normal individuals on whom we determined ratios, but such differences were too small to lead to any appreciable effect. They were obscured by the variability of kidney action. In any single case it is only gross differences in the size of the kidneys which can be detected.

We have been dealing hitherto with normal kidneys. But in the diseased kidney the weight or the size cannot be taken as a measure of capacity, for part of the renal tissue may be functionally inactive. What is needed here is a measure of the amount of renal tissue which remains capable of active work. An anatomical estimate of this sort will only be reasonably correct under certain favorable conditions. In many acute pathological states the methods at present used in histological work give little or no idea of the amount of tissue which has ceased to function, and on the other hand, some conditions associated with strikingly abnormal anatomical pictures are not necessarily combined with great functional deficiency. But this is not true of all anatomical lesions. Varying doses of uranium produce varying degrees of degeneration or necrosis in the terminal portion of the proximal convoluted tubule—the site of urea excretion—and it is possible to make a roughly quantitative classification in such cases in accordance with the amount of secreting tissue involved.

Classifications of cases of uranium nephritis according to the extent of the anatomical change and to the degree in which the ratio was depressed were found to agree (20). This may be considered as evidence of the dependence of the ratio on the size of the kidney, if the word "size" is considered as applying only to actively functionating renal tissue.

So far then as our present knowledge reaches it would appear that there are two main causes determining the magnitude of the ratio, one, a constant, the amount of normal kidney structure, and the other, a variable, the state of activity of the kidney cells, which there is some reason to suppose may vary with the balance between adrenalin and pituitrin in the blood.

The problem resolves itself into the determination of the conditions under which this variable factor becomes constant or relatively constant. The ratio might then be taken as a measure of the amount of active kidney tissue present not only in groups of individuals but in single cases. This would give us what we most need in clinical work—an anatomical foundation for early diagnosis, prognosis and treatment. For functional studies have in the last resort no fundamental significance unless they are of such a nature that structural inferences may be drawn from them.

One essential factor in the conditions necessary before the ratio can be regarded as indicating the size of the kidney has already been made clear. The ratio was not found to be decreased after the removal of one kidney except when the remaining kidney was subjected to a marked strain on its excretory function. The ratio itself then is no measure of kidney size, but only the ratio after the administration of a large quantity of urea. This is a principle so obvious that it does not require elaboration. We could as little expect to estimate the muscular strength of two individuals without imposing a task which called for all their energy, as we can hope to measure the functional capacity of their kidneys apart from conditions requiring the maximum activity of all their renal tissue.

SUMMARY

1. The ratio between the urea content of the urine and of the blood expresses the number of times by which the urea excreted in the urine during a certain period of time exceeds the amount of urea present in 100 cc. of the blood supplied to the kidney during this time. It is the relation between the amount of work accomplished by the kidney, and the most important measure of the amount of work the kidney is called on to perform.

2. Ratios measured over periods of twenty-four hours are constant in normal individuals who have the same blood urea concentration. The normal kidney is therefore not characterised by any intrinsic tendency towards variability of function. Variations in kidney function arise from differences either in the environment or in the anatomical structure of the kidney.

3. Ratios measured over short periods of time vary widely even though the blood concentration be the same. This variability must be due to short lived alterations in environment which counterbalance one another over long but not over short time intervals, for it can be shown that such anatomical differences as may exist between the kidneys of young healthy adults do not play any appreciable part in its production.

4. Differences in the concentration of urea in the urine are not the cause of this variability in the ratio over short periods of time.

5. Evidence is given against the supposition that this variability arises from such alterations in the amounts of urea or of oxygen brought to the kidney as would be produced by differences in the rate of flow of blood through the kidney. Reduction of kidney blood supply below a certain minimum has a marked effect on the ratio, but it does not follow that alter-

ations above that critical amount would have much if any effect.

6. Since it is possible to increase the ratio by the subcutaneous administration of adrenalin and to decrease it by pituitrin, the hypothesis is advanced that part of the variability of the ratio for one hour periods at the same blood urea concentration, may be due to alterations in the adrenalin pituitrin balance in the blood.

7. It is shown that the magnitude of the ratio increases with increase in the blood urea concentration. In other words the kidney responds to a call for more work by an increase in output which is greater than the increase in demand.

It is further shown that the relative variability of the ratio at different levels of blood urea concentration decreases the higher that level rises. In other words the greater the demand for work, the more constant does the rate of work of the kidney become.

Both of these phenomena may be brought into relation with the hypothesis of a regulation of kidney activity by means of the balance between adrenalin and pituitrin in the blood.

8. There is evidence that a direct relationship exists between the magnitude of the ratio and the size of the kidneys. This has been shown by comparing the average ratios obtained from species possessing kidneys which differ widely in size. The removal of one kidney leads to a depression of the ratio. In kidneys whose effective size has been reduced by necrosis or degeneration of varying extent, there is a relation between the degree of depression in the ratio and the amount of tissue which has been rendered functionless.

9. This direct relation between the magnitude of the ratio and the amount of actively functionating kidney tissue is only demonstrable under conditions in which the kidney is called on for the maximal activity of all its secreting elements and is subject to the least degree of variation in rate of work. The ratio can be taken as an approximate indication of the size of the kidney only when it is determined during the strain induced by the administration of a large quantity of urea.

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THE OPERATIVE TREATMENT OF URETHRO-RECTAL FISTULA. PRESENTATION OF A METHOD OF RADICAL CURE

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Urethro-rectal fistula is regarded as rather rare, but is one of the most difficult problems a surgeon is called upon to cure. The lesion is reputed to be most intractable to treatment, a reputation well borne out by a review of the literature from the time of Astley Cooper to the present. The patient who is the victim of such a condition, while not necessarily in danger of his life or subjected to great pain, is usually wretchedly miserable; in fact life may become an intolerable burden. With these characteristics of the lesion in mind, we have felt justified in making a further report of our experience in the use of an operative method for recto-urethral fistula first published (1) in 1913.

Since it is the primary purpose of this paper to describe an operative technique and to relate the results of its clinical application, no exhaustive consideration of the lesion itself, from the view-point of etiology, pathological anatomy, or symptomatology will be attempted. Instead the following summary of the facts presented by our own cases that bear on these general questions is collected here from the appended case reports.

The three general causes of urethro-rectal fistula are trauma, including of course surgical interventions, inflammations, and the destructive ulceration at times associated with malignant growths. All of the eleven cases detailed in this article belong to the first group, and in each instance the trauma was in the nature of a surgical operation. These operations comprised one perineal lithotomy (case 3), four incisions for drainage of prostatic abscesses (cases 2, 7, 9, and 10), and six attempts at perineal prostatectomy (cases 1, 4, 5, 6, 8, and 11). In a twelfth case, not reported in detail for reasons to be explained now, the fistula was of spontaneous origin, due to tuberculosis of the prostate gland, and hence falling into the second group of causes mentioned at the beginning of this paragraph. This patient was generally tuberculous, having pulmonary lesions well marked, bilateral tuberculous epididymitis, tuberculous prostatitis, with the urethro-rectal fistula, and an old arthritis of the left hip joint with ankylosis. His fistula made him utterly miserable and it was at his own insistence, perhaps against better surgical judgment that the operation was undertaken. Mechanically the difficulties were greatly aggravated by the ankylosed hip, which interfered with good lithotomy position on the table. However, the patient stood the procedure well and it was apparently successful, the wound healing nicely and urine passing per urethram without leakage backward, when in the third week after operation he suddenly died from an acute peritonitis due to rupture of an extensive tuberculous abscess of the abdominal lymphatic glands. The case is therefore inconclusive as to the operative procedure here under discussion and is not included formally in our report. We have seen no cases of fistula due to malignant growth, and of course such cases would not be suitable to our operative treatment in any event.

The pathological anatomy of these fistulae may be dismissed with brief comment. In practically every instance the urethral orifice was in the membranous portion of the urethra, the tract itself very short and straight and the rectal orifice in the anterior wall of the rectum, about the mid-line, and within a short distance above the internal sphincter muscle. In two cases, however (3 and 9), the fistula opened from the prostatic urethra and passed through the prostate gland. This may account for the unsatisfactory result in case 9, the only one of the series that may be considered a failure. In addition to the recto-urethral fistula, there was a communicating perineal fistula in cases 6 and 8, and in the latter there were two large abscess cavities in the perineal tissues connected with the fistulous tracts. In cases 3 and 10, the vesical sphincter was also damaged, and in the second of these cases a very successful repair of this muscle was added to the usual operation. In several cases the anal sphincters had been damaged, as case 1, causing loss of rectal control. This was also successfully repaired. In every case the perineum was more or less extensively scarred and indurated.

The symptoms presented by these patients were those obviously dependent upon the mechanics of the lesion. Prominent of course—indeed diagnostic—is the escape of urine into the rectum, and the passage of gas and fecal matter through the penis. Those cases in which the bladder sphincters were injured experienced more or less constant dribbling of urine into the rectum. When this lesion was not present the abnormal exit of urine was noticed only on voiding. Gas may escape at any time through the penis, whereas fecal material usually only appeared at defecation or when the intestinal contents are partially liquid. The diagnosis, in view of the history, symptoms and urological and rectal examinations, usually is obvious.

No attempt will be made to narrate the various procedures, ranging from simple cauterization to complex operations with plastic flaps, that from time to time have been advocated for the cure of urethro-rectal fistulae. In Tuttle's "Diseases of the Anus, Rectum and Pelvic Colon" may be found a full consideration of this phase of the subject. A few publications more or less similar to ours will be referred to, after the description of the method used in our cases, and the presentation of the case reports.

The operation may be described briefly as follows. First, suprapubic drainage of the bladder is established, with the patient in dorsal posture. The patient is then shifted to the exaggerated lithotomy position. A racquet shaped incision, beginning in the mid-line of the perineum about 3 cm. anteior to the anal margin is carried backward to this margin, and then encircles it at the muco-cutaneous juncture (fig. 1). Through the circular part of this incision the mucosa of the rectum is dissected free all around (fig. 2) until a cylinder of the membrane is stripped from its attachments well above the point at which the rectal orifice of the fistula opens, the fistulous tract, of course being divided transversely in this process (fig. 3). This ascending dissection of the bowel is carried upward until sufficient mucous membrane is loosened to permit the pulling of the segment containing the fistulous orifice well out of the anus, the orifice and a small margin of normal mucosa above it, and all that below it, lying outside the skin level and later being excised. This part of the procedure may be described as an exaggeration of the Whitehead principle in operating for hemorrhoids.

A minor point of some practical importance consists in beginning the dissection of the mucosa at the posterior or dorsal part of the circle. Not only is it easier to find normal planes of cleavage here, where there is no scarring, but the field is less obscured by hemorrhage than would be the case if the anterior side is first attacked, as blood then runs down over the posterior half of the anus.

Next, the structures of the perineal body are divided through the straight incision in the mid-line—the handle of the racquet—so as to expose thoroughly the urethral orifice of the fistula (fig. 4). It should be noted here that in the first three of our cases the sphincter ani muscle had been cut in the mid-line anteriorly in previous attempts at cure of the condition, so that this part of the incision actually divided nothing but scar tissue in these cases. This scar tissue in such cases is dissected away laterally sufficiently to expose the ends of the sphincter ani muscle, the levatores ani, and the lesser muscles of the perineal floor. In the rest of the cases with one exception, the intact sphincter ani muscle was divided in the mid-line anteriorly to allow a better exposure and repair of the urethral opening, and the muscle then repaired as in the first three cases. In case 7 it was not considered necessary to cut the sphincter at all. The edges of the urethral fistulous opening then exposed are freshened, and brought together with catgut sutures over a sound which has been previously passed through the urethra. These sutures do not penetrate the surface of the urethral mucous membrane. The levatores, fascia, and smaller muscles are then brought together by interrupted catgut sutures across the mid-line of the perineum in several layers, reconstructing the perineal body much as is done in gynecological operations for relaxed vaginal outlet (fig. 5). Finally, the sphincter ani is restored by uniting its ends with a mattress suture of catgut, and the mid-line incision is closed with interrupted sutures (fig. 6). The last stage in the operation consists in the excision of the protruding cuff of rectal mucosa in which the fistulous opening lies, and the union of the lower end of the rectal tube to the anal skin margin (fig. 7). This is done by interrupted silk sutures after four submucous-subcutaneous sutures of catgut have placed at quadrant points to help anchor the bowel in place.

It will be seen that there are four essential principles in this procedure. The first is the protection of the repair from leakage and muscle-spasm by diverting urine from the urethra through suprapubic drainage. This has been emphasized in the publication of a previous operation for the same purpose by one of us (Young). The second principle is the complete ablation of the damaged portion of rectal wall and the reposition of perfectly sound mucosa quite to the skin edge. The third element in the operation is the closure of the urethral orifice, and the final essential is the interposition between rectum and urethra of a solidly built up perineal body.

The histories of our cases follow.

Case 1, W. A. M., age 26 years. Family and past history not important except as herein related. Gonorrhoeal infection in July, 1905, the discharge lasting about two months. Recurrent infection in summer of 1907. In spite of various treatments, the patient continued to have trouble, especially from prostatic involvement. An attempt at perineal prostatectomy in June, 1909, made in Nashville, Tenn., to relieve this condition, resulted in producing a urethro-rectal fistula.

The patient was operated on three successive times in the summer of 1911, in Chattanooga, Tenn. The first attempt consisted in cauterization of each of the fistulous orifices. At the second operation the fistulous tract was split through a mid-line perineal incision, the levator and sphincter ani muscles and the rectal wall being divided. As a result of this, the fistula was much enlarged, but its rectal orifice was brought down nearer the skin edge than it had been. The third trial consisted in an attempt to turn a flap over the fistula and reconstruct the sphincter ani. This was a complete failure.

Condition in January, 1913. Patient complains that when he voids, practically all urine escapes through the rectal fistula, unless he closes it by pressure of finger over orifice. There is incontinence of gas and fluid stools, and these occasionally escape, in part, through the penis. On examination there is a depressed scar of old suprapubic incision in mid-line of lower abdomen. Perineum shows an inverted horseshoe shaped scar. The anus is dilated widely, has a scar in mid-line anteriorly and when patient attempts to contract sphincter, it is evident that there is no muscle left except around the posterior three-fourths of the circle. Just within the rectum, in the mid-line anteriorly, one feels the rectal orifice of the fistula, about 5 mm. in diameter. Prostate small and adherent. Perineum one mass of old scar tissue.

Operation January 27, 1913, Dr. Young and Dr. Stone. The operative steps as described above were executed successfully. Some difficulty was experienced both in opening the bladder for suprapubic drainage, and in dissecting the anterior wall of the rectum, because of dense scarring from previous operations. The patient left the table, however, in good condition, and with a very satisfactory repair. Convalescence was quite uneventful. The suprapubic tube was removed after two weeks, and in six weeks this wound was firmly healed There never was any leakage from the urethra after operation. The rectal wound healed well. The patient regained excellent control of the rectum with repair of the sphincter muscle, and when examined for discharge March 15, 1913, could be conservatively considered entirely cured, with urination and defecation normal. A letter from this patient in the autumn of 1914, describes his condition as most satisfactory. The fistula has never reopened and he has good sphincter control.

Case 2, O. T. B., age 48 years. The essentials of his history follow. As a result of post-operative catheterization, his bladder and urethra became infected with staphylococcus in 1903. Consequent to this infection, which persisted in spite of treatment, a prostatic abscess developed. This was drained through a semilunar perineal incision, at which operation the rectum was inadvertently injured, and thus a urethro-rectal fistula established. The perineum was incised to the fistula, and the sphincter ani divided in an effort to cure the condition in 1907. This, however, was unsuccessful and another attempt was made in 1911, which likewise failed. When the patient presented himself for examination in April, 1913, the following facts were observed. About an inch and a half above the muco-cutaneous margin there is a small fistula, admitting only a fine probe, which passes from the rectum into the mid-prostatic urethra. When the patient voids, about four-fifths of the urine passes through the natural channels and about one-fifth through this fistula. The perineum has been divided in the mid-line, and shows much scarring. The sphincter ani muscle had also been divided, but its ends have united without much retraction, so that there is fairly good control.

Operation April 4, 1913. The same steps were followed out, as described above. In this case the tissues of the patient were much more fibrous and difficult to dissect, but finally the operation was completed successfully, the rectal cuff drawn down well and excised with the fistula.

Postoperative history uneventful except that some oedema developed about the line of suture on the fifth day. On the fourteenth day the patient was allowed to be out of bed and the suprapubic drainage was withdrawn. On this day the patient thought that he passed a few drops of urine through the line of suture at the muco-cutaneous margin. This day and the next, however, he was carefully watched while voiding after the operative wound had first been dried. There was absolutely no escape of fluid of any sort, so that the fistula was considered closed. The patient was discharged on the sixteenth day, at his own urgent request, although we should have kept him longer if possible.

An examination of this patient in April, 1915, gave the following results. At times the patient still has some leakage of urine at the anal margin, the opening apparently being at the muco-cutaneous line in front. It is, however, too small to see or feel. The patient was under observation four days. During two days there was absolutely no leakage; at other times only a few drops. The largest leakage observed was when the patient voided 250 cc. per urethram and lost 5 cc. per anum. The patient has good control of both anal and vesical sphincters and sleeps in a dry bed now, whereas before the operation this was impossible. His condition was so greatly improved that it was decided, with his full concurrence, not to try any further operative treatment.

Case 3, H. M. D., age 23 years.[1] The essential facts in the history of this case are as follows. The patient was operated on in 1900 by the perineal route, for stone in the bladder. During the operation the rectum was wounded and the patient recovered with a recto-urethral fistula and rectal incontinence. In 1903 and 1904 operations were undertaken to cure the fistula, but without success. In 1906 he was operated on again; this time the damaged sphincter ani being repaired successfully, but the fistula was not cured. A fourth operation was done in 1908, again without success. In one of the operations, the patient does not recall just which, suprapubic drainage was employed.

Condition on April 9, 1913. During the day, urine slowly leaks from bladder into rectum, from which it is evacuated every two to three and a half hours. In addition patient has a regular well formed bowel movement daily. At night when asleep the urine accumulates in rectum until it overflows through anus, with fecal matter, soiling bed. General health good. It is the inconvenience of his condition that chiefly concerns the patient.

Examination. Scar of old suprapubic incision in mid-line of lower abdomen. In the perineum is an inverted V-shaped scar, well healed, and a linear scar in the median raphé also. The mid-line of the anal ring anteriorly is a mass of scar tissue, but the sphincter functions fairly well. About 2 cm. above the muco-cutaneous margin of the rectum is an opening in the anterior wall admitting a medium-sized probe, which passes then through the apex of the prostate gland and into the urethral just below the neck of the bladder. When the probe is advanced slightly it enters the bladder, and urine trickles out along the instrument.

Operation on April 10, 1913. Same steps as above described. The dissection in this case was easier than in case 2, but the urethral orifice was much higher, practically involving the vesical sphincter. Repair was made without inordinate difficulty, however. Convalescence was uneventful. The suprapubic drainage was removed in fourteen days, and the patient left the hospital in twenty-one days entirely well, the recto-urethral fistula being completely cured, and the sphincter control practically normal. There is a slight tendency to escape of urine through urethra when the bladder is overdistended, and the suprapubic wound is not yet entirely healed. Otherwise the patient presents a restoration to normal. This patient was heard from in the autumn of 1914. His condition is entirely satisfactory except that the vesical sphincter is somewhat weak. With a full bladder there is still a tendency to dribble urine per urethram. The fistula has remained entirely closed and the anal sphincter is competent.

Case 4, E. F. S. Admitted to the Johns Hopkins Hospital February 15, 1915, with a diagnosis of benign prostatic hypertrophy. The patient was operated on for this condition by the perineal route on February 24 by one of the resident house officers. A week after the operation it was discovered that there was a communication between the rectum and the perineal wound—that fecal material discharged through this fistula. On March 8 suprapubic cystotomy for drainage was done. For several days after this fecal material came through the suprapubic wound. On April 8 a note was made that at times there was a considerable amount of fecal discharge through the urethra. By April 15 the suprapubic wound had closed. By the middle of June the perineal fistula had closed, and the patient was left then with a simple recto-urethral fistula. On the 28th of June the typical operation as above described was carried out, with less difficulty than usual except for the friability of the mucous membrane. Following this operation the patient made an uninterrupted recovery, and on July 28 the following note was made when he returned to the hospital for inspection. "The perineal incision is well healed, as is also the rectal wound. There is no fistula. Slight stenosis of anal outlet at circular scar. Closure apparently quite solid. Sphincter somewhat relaxed, but still functions well. Operation successful." On August 7 the patient again returned for observation, at which time no new finding was added to the above note.

Case 5, A. B. Entered the Johns Hopkins Hospital April 8, 1915, with a diagnosis of benign prostatic hypertrophy. Prostatectomy by the perineal route was done on April 13, and on May 26 for the first time it was discovered that there was a recto-urethral fistula, when an attempt was made to irrigate the urethra and the fluid passed into the rectum. There had never been any other evidence of the existence of this fistula. An examination made now disclosed a longitudinal tear discovered in the mid-line in front. The patient was discharged from the hospital on June 22. He returned to the hospital for treatment of the fistula, and on October 21 the following note was made. "Slight induration of the internal sphincter and slit-like orifice in the anterior rectal wall about 5 mm. in length, extending longitudinally upward from the level of the internal sphincter. The edges are indurated and there is considerable surrounding fibrosis. On October 22 the usual operation for cure of recto-urethral fistula was done without much difficulty. The patient made an uneventful recovery and was discharged on November 27 with the following note. "Anal sphincter is of good tone. Slight irregularity of the muco-cutaneous junction. Rectum is perfectly intact throughout. Fistula entirely closed." Patient returned again for inspection December 7, at which time no additional facts were noted.

Case 6, R. G. Admitted to the Johns Hopkins Hospital August 24, 1915, with a diagnosis of recto-urethral-perineal fistula. His past history is unimportant except as follows. About eighteen months ago he was operated on in another hospital for enlarged prostate by the perineal route. The patient has had since that time a recto-urethral fistula. On August 30 the usual operation for recto-urethral fistula was done. Because of the discharging orifice in the perineum, it was necessary to excise a certain amount of surrounding skin and subcutaneous tissue to get fresh surface for healing. The patient was discharged from the hospital on October 11 with the following note. "Suprapubic wound is completely healed and so has the perineal wound, except for a fistulous opening in the anterior portion of the mid-line. At each voiding there is considerable discharge of urine through this opening. Patient has passed no gas through the urethra since operation nor any urine into the rectum. The rectal sphincter is somewhat relaxed, but mucous membrane is perfectly intact. There is no fistula." On November 23 the following note was made. "The perineal fistula still remains open and a few drops of urine escape at each voiding. On examination today the perineal fistula's opening is almost closed, being extremely small and little larger than a pin head. There was no communication with the rectum." The Out-Patient Department subsequently reported the closure of the small perineal fistula.

Case 7, J. T. Admitted to the Johns Hopkins Hospital October 26, 1915, with a diagnosis of recto-urethral fistula. Three years ago patient was operated on for prostatic abscess, by a perineal incision. When this wound healed he was left with a recto-urethral fistula. On examination the following special note was made. "About 1 cm. anterior to the anal margin is seen the scar of old operation with slight pin hole sinus present. Slight external hemorrhoids. Anal sphincter of good tone. Just inside of anal sphincter can be felt a depression surrounded by fibrous scar which will not admit tip of index finger. This is in all probability the opening of the recto-urethral fistula. This point is slightly to the right of the mid-line in front." On October 29, 1915, the typical operation was carried out with the exception that in this case it was not deemed necessary to divide the anal sphincter muscle. Patient's convalescence was uninterrupted following the operation except for the formation of a rather large hematoma to the right side of the rectal wound. He was discharged from the hospital November 27 as well, and returned on December 9 for inspection, when the following note was made. "The suprapubic wound has healed solidly. No urine escaped from it during the past week. The urine is voided every two or three hours during the day and once at night. Urination is free and accompanied by no pain. There is no escape of urine either from the rectum or perineum. On examination today the wound about the anal margin has healed. A few mucus tags protrude at the site of the hematoma. The functional result is excellent."

Case 8, G. D. J. Admitted to the Johns Hopkins Hospital March 25, 1916, with diagnosis of recto-urethral fistula. A perineal prostatectomy had been done elsewhere in October, 1914. Wound did not heal and urine drained into rectum. In December, 1914, an attempt at closure had been made. This was unsuccessful, as was a second attempt in December, 1915. Examination on admission showed the following condition. "Globus major on either side about twice normal size, moderately indurated and tender. In perineum there is extensive scarring and induration of previous operations. Surface of perineum is quite irregular from this cause and there is a small urinary fistula which is draining at present. Anal sphincter of good tone. There has been a prostatectomy, and in region of the prostate there is marked scar formation. Mucosa of rectum is densely adherent anteriorly. About 2.5 cm. inside the sphincter, and just opposite the membranous urethra can be felt a small opening anteriorly, which admits a probe."

On April 7, 1916, the operation for radical cure of the recto-urethro-perineal fistula was performed. The usual steps of operation were followed, with certain additions made necessary by the peculiarities of this case. The area of scarring in the perineum was excised by a more or less oval incision, including the opening of the perineal fistula. This exposed two old abscess cavities, on either side of the mid-line opposite the tuberosities of each ischium, containing large amounts of granulation tissue. These were completely excised, which left a considerable defect in the soft parts of the perineal floor. With some difficulty flaps were dissected to form a closure in the repair stages of the operation. Otherwise the case was handled along the usual lines of procedure.

The post-operative history of this case was not quite as satisfactory as in most of the others. When the bowels were moved for the first time on April 16th, the repair of the rectum and perineum gave way in part and some fecal matter appeared in the opened perineal wound, and on April 24th urinary leakage in the perineum developed. The Davis suction drainage was applied to the suprapubic wound, and continued until July 2. The bladder was irrigated daily. The perineal wound was frequently irrigated and dressed. On July 2d the patient was allowed up and about and on July 8th all suprapubic, perineal and rectal leakage of urine had ceased. All urine passed per urethram. Patient voids every one and one-half hours. Rectal wall and sphincter well healed. No fecal discharge through perineum or urethra. Sphincter action good. Perineal wound not entirely healed. The patient was discharged from the hospital, and wrote several months later saying that all his wounds were healed, the fistula entirely closed, and his condition good.

Case 9, J. A. Admitted to the Johns Hopkins Hospital on May 23, 1916, with diagnosis of recto-urethral fistula. Following recurrent attacks of specific urethritis, the patient developed an acute prostatic abscess in 1914. This was incised in Philadelphia, apparently per rectum. His acute symptoms were then relieved, but there followed a recto-urethral fistula with the escape of gas through the penis and of urine into the rectum. Five months later an internal urethrotomy and dilatation of the urethra to 34-F was performed. Somewhat later the fistulous tract was apparently curetted. Neither of these procedures accomplished a cure of the fistula.

Examination. Anal sphincter somewhat relaxed. No scar in perineum. Just above the internal sphincter there is a curious circular fold or band of scar tissue, running from the prostate laterally, particularly to the right. To the right of the mid-line an opening in the anterior wall of the rectum can be seen. A fine probe, passed through this opening, travels forward toward the prostate and urethra, and causes referred pain to the penis and perineum. There is some general induration of the anterior wall of the rectum and of the prostate.

Operation June 5, 1916. The usual operation was executed, the only matter of note being that the fistula ran through the apex of the prostate and its course was surrounded by a cheesy, sebaceous-like material suggesting an old inspissated abscess. The actual urethral orifice was not sutured, but healthy tissues were sutured over it, and the closure otherwise carried out as usual.

The patient was discharged on the thirty-fifth day. Small amounts of urine—from a few drops to a teaspoonful—have been coming through rectum when patient voids, since the suprapubic wound healed. The suture line of rectal edge to skin at anterior mid-line had pulled away a little and apparently this was where the leakage occurred.

Case 10, C. C. Admitted to Johns Hopkins Hospital April 2, 1916, with diagnosis of recto-urethral fistula. Patient had a perineal operation for prostatic abscess performed three years before, following which he developed a recto-urethral fistula. Two operative attempts made elsewhere have failed to close the fistula. Present condition. Patient complains of passage of gas and occasional fecal material through penis, and during the night accumulation of urine in rectum. There is also constant dribbing of urine from urethra when patient walks or stands, showing incontinence of bladder sphincter. Examination shows linear scar in perineum about 4 cm. in length. Anal sphincter possesses good tone. There is induration of tissues in front of rectum particularly just below the apex of the prostate gland. At this point there is some tenderness on pressure and a slight palpable dimple. Into this dimple a probe can be passed for a short distance forward. This is probably the rectal orifice of the fistula. The urethroscope shows the vesical orifice dilated and internal sphincter of the bladder relaxed. On April 5, 1916, the usual operation was performed, with one additional step of much interest. During the first portion of the procedure, when the bladder was opened for suprapubic drainage, Dr. Young did a plastic repair of the internal sphincter of the bladder and the internal urethral orifice. He is to report this in detail in connection with other similar cases. The perineal dissection was carried out in the usual way except for unusually extensive scar removal. The usual repair was then done. After a remarkably smooth convalescence, the patient left the hospital on May 6, 1916, entirely healed. Not only was the urethro-rectal fistula quite closed, but urinary continence was restored. The patient had no dribbing, voided only every 4:5 hours, and had excellent control. This patient was seen for review six months later and found to be in every way satisfactory.

Case 11, E. M. Admitted to Johns Hopkins Hospital January 16, 1917, with a diagnosis of urethro-rectal fistula. An attempt had been made at a perineal prostatectomy in Arizona in 1915. After this he was left with a urethro-rectal fistula, passing gas and feces per urethram and urine per rectum. In May, 1916, an operation was performed elsewhere in an attempt to cure the fistula. This was unsuccessful. On examination the following note was made. "Anal sphincter of good tone. Fistulous orifice in anterior rectal wall about 2.5 cm. above anal margin. Perineum is indurated from old scar tissue, and the whole area of the prostate is fibrous."

Operation January 29, 1917. The usual steps were carried out without any change worth noting. During convalescence the perineal incision broke down in part, but there was never any leakage of urine into the bowel or perineum, and no breaking down of the essential repair. The patient was discharged on March 9, 1917, with the following note. "Several remaining black silk sutures removed. Wound cleaned up well and nearly healed. Sphincter ani holding firmly. No escape of gas or feces per urethram. No urine leaks into rectum, fistula cured."

It will be seen, in brief review, that these cases presented many difficulties. Some of them were of long duration, so that the fistulous tract had become thoroughly organized into dense cicatrix. They had all been subjected to one or several previous operations, rendering the whole region abnormal and extensively scarred. In three cases the sphincter ani had been previously damaged, so that to the fistula itself was added disturbance of the rectal outlet. In all of these cases, with the exception of case 9, belonging in a class admittedly recalcitrant to treatment, and indeed declared by the older writers to be well nigh hopeless of betterment, a most gratifying degree of success was attained. We hope that a method which has served so well in this small series of cases will be subjected to further trial. And with this hope we wish to add a perhaps needless admonition. As in all plastic work, it is essential that free mobilization be secured, so here the rectum must be freed well above the fistulous tract before an effort is made to bring it down to the skin edge.

Ziembicki (2) in 1889 is the first author whom we have been able to review, who has at all approached this method of attack. He, too, loosened the rectum from its lower attachments. But instead of removing the fistula-bearing lower cuff of bowel, he simply sutured the openings in the urethra and rectum and then rotated the rectum somewhat to one side, so as to bring the two orifices out of line with each other. We believe our procedure possesses obvious advantages. Paul Segond (3) in 1902, applied the principle of pulling down the rectum in attacking recto-vaginal fistulae, and in 1903, Tedenat (4) reported having successfully operated on two cases by dilating the anus, dissecting up a cuff of rectal mucosa, closing the urethral orifice thus exposed; and then pulling the rectal mucosa down so that the rectal orifice of the fistula is brought to the anal margin. Elting (5) has adopted an analogous attack upon ordinary fistula in ano.

We were not acquainted with the paper of Tedenat until after three of our cases had been operated upon and we were considering their publication. (1). Unquestionably we are not the first who have realized the applicability of the "Whitehead principle" to the cure of such fistulae as are the subject of this paper, but we desire to emphasize the importance also of the other steps involved in our procedure, the combination of all of which we believe has been the secret of success in these extremely difficult cases. It may be urged that the magnitude of the surgical undertaking is out of proportion to the extent of the lesion. We have but to call attention, in reply, to the fact that many of these patients had undergone previous operations without success, yet their condition was such as a result of the fistulae, that they very gladly submitted to any proposed method of securing relief.

REFERENCES

(1) Young and Stone: Transact. Amer. Assoc. of Genito-Urinary Surgeons, 1913, p. 270.
(2) Ziembicki: Congres Francais de Chirurgie, 1889, iv, p. 295.
(3) Segond, Paul: Thesis. Paris, 1902.
(4) Tedenat: Montpelier Medicine, 1903, xvi, 81, 114.
(5) Elting: Annals of Surgery, 1912, p. 744.

PLATE 1

Fig. 1. The racquet shaped incision beginning at the midpoint of the perineum and extending posteriorly encircling the anus at the muco-cutaneous juncture.

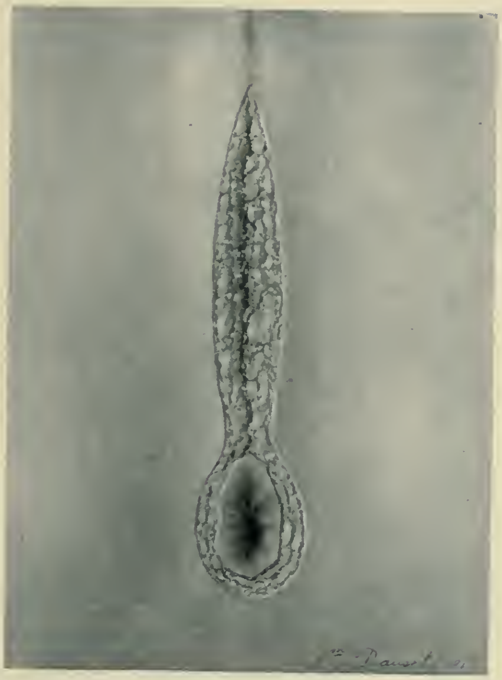

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PLATE 2

Fig. 2. The first in the freeing of the rectal mucosa from the underlying structures.

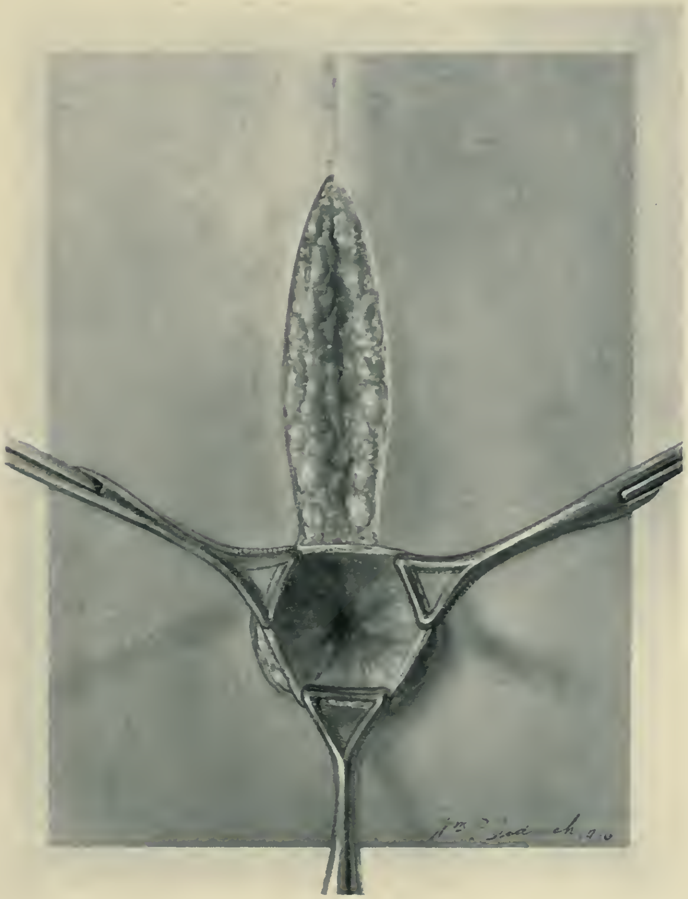

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PLATE 3

Fig. 3. The mucosa has been freed to a point well above the fistulous opening and the sphincter ani muscle has been divided.

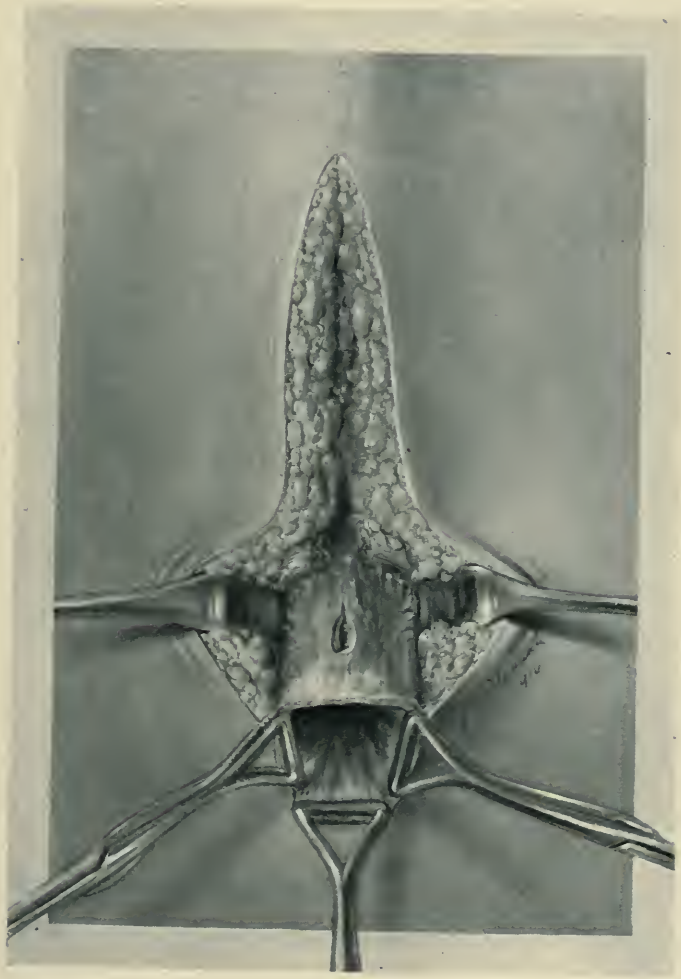

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PLATE 4

Fig. 4. The dissection has been carried down through the perineal body and the urethral orifice of the fistula exposed.

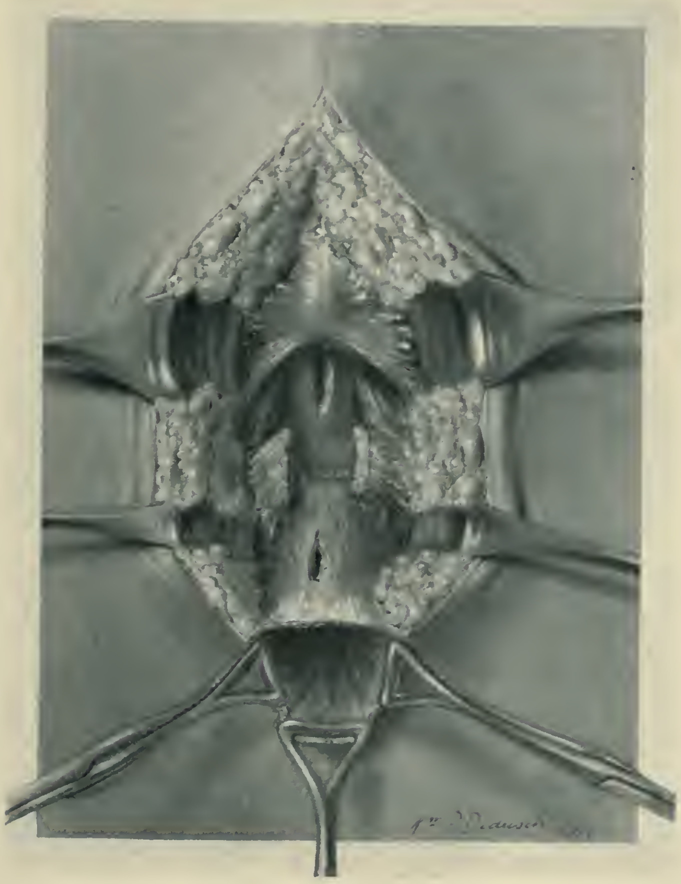

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PLATE 5

Fig. 5. After freshening its edges, the fistulous opening in the urethra is closed and the perineal musculature is brought together with interrupted sutures. The cut edges of the sphincter ani are approximated.

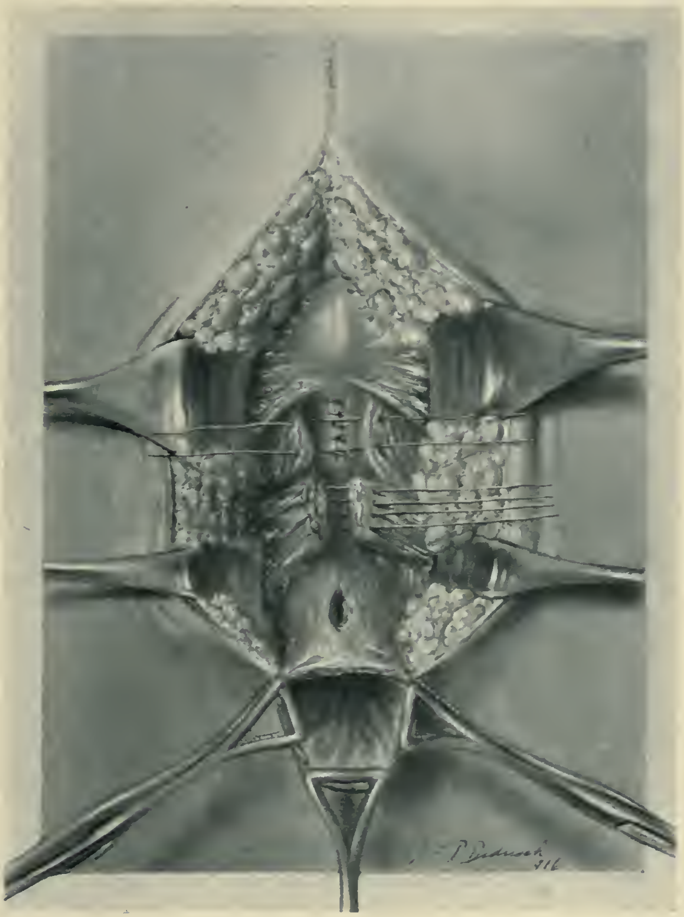

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PLATE 6

Fig. 6. The final stage of the operation consisting of the amputation of the cuff of mucosa containing the fistulous opening after which the lower end of the rectal tube is united to the anal skin margin.

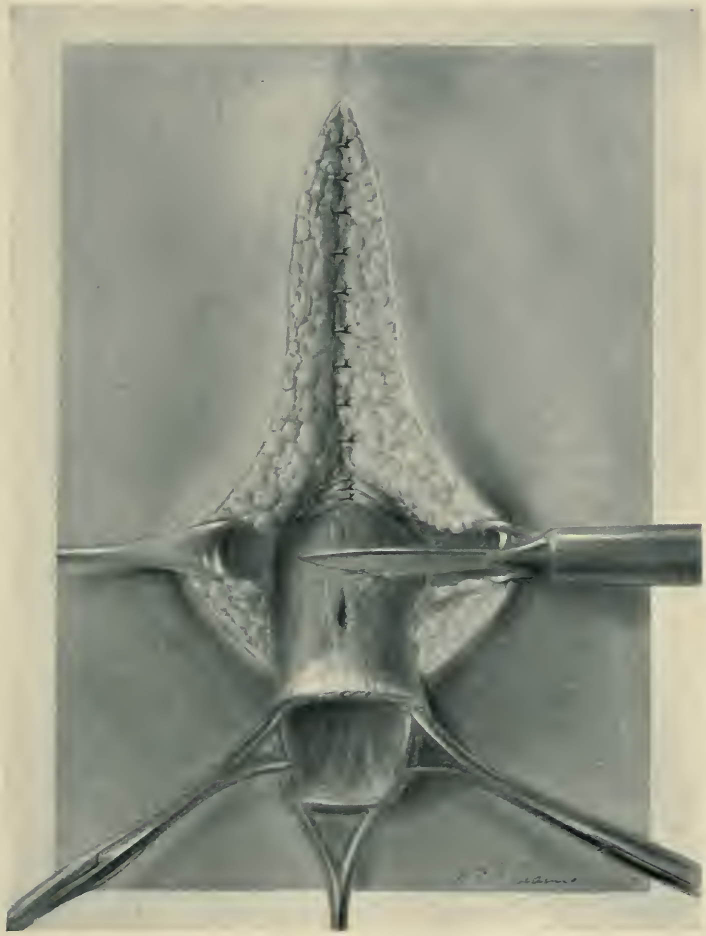

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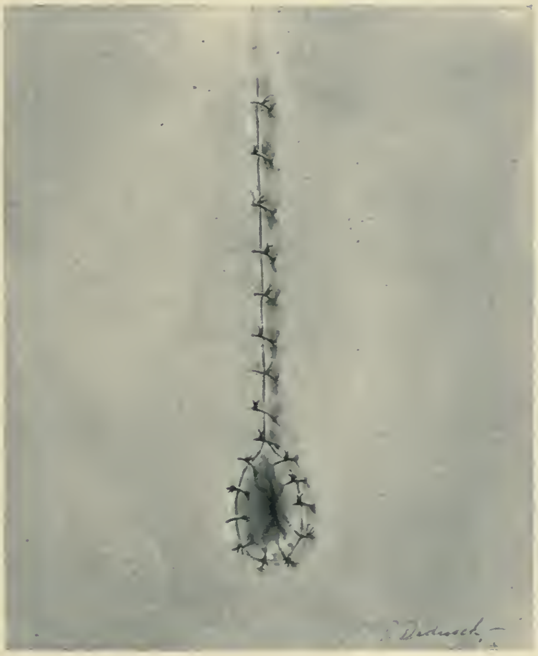
PLATE 7

Fig. 7. The final approximation of the skin.



7

THE USE OF TESTS OF RENAL FUNCTION IN CASES OF NEPHRITIS[1]

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In recent years medical interest has been centered more on function than on structure. With the kidney our earlier interest in anatomical structure, though continued, has become less a question of study and discussion because our interest in renal function has been increased greatly as a result of the development of tests to measure it. In considering a patient with a diseased kidney the clinician is interested primarily to know how well can the kidneys perform their duty as excretory organs and how long is it likely that their function, though decreased, is going to meet the demands of that particular individual. It is of value to know that the kidneys are sclerosed but it is of far more importance to know that renal function is reduced already to one-quarter of the average normal; that this reduction appears to be steadily progressing; and that of the various excretory activities of the renal parenchyma, as an example, elimination of sodium chloride is most imperfectly carried out.

With the view of knowing the functional capacity of the kidney in a given individual numerous tests of renal function have been devised. Some of these soon have shown that they were unsatisfactory and have been discarded. Others, though quite satisfactory in their results, have been too cumbersome or their use has been too unpleasant for our patients, and they have been discontinued. A few are reasonably simple and easy of execution so far as the patient is concerned. These have been used most extensively. None of them is perfect, and continued investigation ought to yield better ones. Some have been advocated with undue enthusiasm and while very valuable have failed to yield the results claimed for them in the beginning.

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[1] An address delivered before the Buffalo Academy of Medicine, February 28, 1917.

Many of the earlier advocates of tests for renal function had the idea that the kidney's selective excretory power might be measured by various tests and from the results obtained an accurate anatomical diagnosis of the distribution of structural changes could be made. So far this has remained impossible and so far as I can see with types of tests now in use, refined anatomical diagnoses on the basis of functional tests cannot be made or is it likely that such results will come soon.

The tests which we are now using for the most part measure total renal function; sometimes they indicate preponderance of injury in one or another of the renal structures; consideration of the principle of selective renal excretion with our tests enables us to subdivide renal cases to a certain extent and serves as a guide in the management of the patients. This latter phase of the problem is probably the one of which we have least knowledge.

I will not burden you with an enumeration of the many tests of renal function that have been described, nor do I expect to discuss the underlying principles of these tests. The tests to which I will refer are the ones which at the clinic of the Peter Bent Brigham Hospital have seemed most useful; they are the ones of which I can speak with first-hand knowledge; doubtless others are equally good; perhaps some are definitely better; a number are quite certainly only different ways of getting the same result and have no particular advantage over the ones we are using. It has been said in regard to histological staining technique, that many new methods are only ways of staining something blue that by a former method just as easily stained red. In this sense some of the duplication of methods of testing renal function has been of no service.

In my clinic after trying a variety of methods of testing renal function, we have come gradually to use the following as best meeting the requirements of ease and comfort of execution and of furnishing such data as we need for the management of our nephritic patients. These methods are:

1. Phenolsulphonephthalein elimination.
2. Determination of the blood urea and the rate of urea excretion. (Ambard coefficient or McLean index.)
3. Determination of specific gravity, sodium chloride and nitrogen content of urine collected in two-hour portions during the day with the patient on a special diet (two-hour test).[2] At night one ten-hour specimen is collected and analyzed. In this test a comparison of the day 24 hour amount with the night 24 hour amount is of value.
4. The amount of diuresis produced by such a diuretic as theocin.

These methods are fairly simple; they cause no great annoyance to the patient; they can be carried out in a short period of observation; they yield information of much service in managing nephritic patients.

In applying tests of renal function we should keep in mind what information we are seeking to obtain from them and whether a given test or some other one is most likely to yield the information sought. All four of these tests may be used in some cases; in others only certain ones can be used; in certain cases not all of them need be used. The tests should help us as to diagnosis, prognosis and treatment; about these we desire and can expect information. Perhaps it will be simpler if I consider these separately and illustrate my remarks with brief abstracts of cases which I have observed.

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[2] In this test at first we used a diet modified slightly from that used by Schlayer and Hedinger (Deutsch Arch. f. Klin., 1914, cxiv, 120). This is described in the Am. Jour. of Med. Sciences (see Studies of Nephritis, Christian, Frothingham, O'Hare and Woods, Am. Jour. of Med. Sciences, 1915, cl, 657). This diet was not palatable for our average patient and so at present we are using a somewhat different diet as follows:

Morning meal: Orange 50 grams, oatmeal 150 grams and milk 25 cc., 1 egg 50 grams, toast 20 grams and butter 5 grams, sugar 10 grams and cream 20 cc. to be used with 150 cc. of tea or coffee.

Mid-day meal: Milk (in soup) 150 cc., steak 75 grams, potato 100 grams and butter 10 grams, peas 100 grams and butter 10 grams, bread 20 grams and butter 5 grams, ice cream composed of milk 100 cc., cream 20 cc., sugar 10 grams and 1 egg 50 grams, sugar 10 grams, NaCl 3.5 grams (to be used by patient on above food) and water 500 cc. with meal.

Evening meal: Tomatoes 75 grams and butter 10 grams, lettuce 20 grams with celery 50 grams and olive oil 20 cc., bread 20 grams and butter 5 grams, baked apple 100 grams with sugar 20 grams and cream 20 cc., water 500 cc. with meal. 250 cc. water during evening.

This diet is similar to one used by Mosenthal (Arch. of Int. Med., 1915, xvi, 733) in a modification of the Schlayer and Hedinger test. Rather wide variations in diets would give very similar results in the sense of showing a departure from the normal curves of excretion when the kidney is diseased. It is well to emphasize this, as the idea that the test is only possible when a very definite diet is used might prevent many from applying the test. Very good results can be obtained with patients on average normal diets in which the noon-day meal contains the largest amount of proteid and sodium chloride.

DIAGNOSIS

So far as I know, the most delicate test of renal damage that we possess is the presence of albumen and casts, leucocytes or red blood cells in the urine in varying combination. They are never absent in all of several specimens on different days if there is renal damage, though single examinations may fail to reveal any even in patients with severely damaged kidneys. Their presence, however, does not justify the diagnosis of nephritis unless supported by other data, though their continued absence justifies us in saying that the kidney is free from nephritis. I use the term "nephritis" here in the sense of a diffuse progressive degenerative or proliferative lesion involving renal parenchyma or interstitial tissue or both. The importance of making repeated examinations of the urine for albumen, casts and cells as the best means of detecting renal damage is obvious from what I have just said.

If these elements (albumen, casts and cells) are found in the urine, how can we prove or disprove the presence of nephritis? Here is where the functional tests help in diagnosis. Although this evening I am going to confine my remarks to tests of renal function I wish to make it clear that the results from them must be evaluated in connection with the information obtained from the patient's history and from general methods of examining patients.

I am one of those who believe firmly that no single test is pathognomonic and that the patient as a whole must be considered every time. He who sits in the laboratory and attempts to diagnosticate and prognosticate in reference to patients is just as likely to make grievous errors as he who seeing the patient puts all reliance on the "tactus eruditus" and the diagnostic "hunch." He who does either to the exclusion of the other is likely to be one whose mind and attitude is of the paper-thin variety of narrowness and with such I have no sympathy. So please remember that throughout my remarks I intend that results from testing renal function are to be interpreted in relation to results obtained by other methods of examination applied to the patients.

From the point of view of diagnosis in most cases of advanced nephritis functional tests are not needed because the patient's condition is quite evident from general methods of examination. However, in the patient who rapidly or suddenly develops partial or complete unconsciousness, probably falls, receiving a blow on his head, and is seen for the first time in a stuporous or unconscious condition, knowledge of the presence or absence of advanced nephritis is of importance but the diagnosis is not easily made. Most such cases show albumen and casts in the urine and their blood pressure is high either as a part of a preexisting vascular hypertension or as the result of increased intracranial pressure. In a series of six cases of this type recently observed in which there was autopsy confirmation of cerebral haemorrhage, all showed albumen, four had casts and all had hypertension, the systolic pressure being as high as 220, 230, 240, 260, 270 and 300 mm. of mercury respectively and yet they showed but little renal lesion. In this type of case we are helped in making an antemortem diagnosis of a cerebral lesion rather than one of uremia by determining the urea nitrogen or total non-protein nitrogen of the blood and finding it within normal limits or but little increased above the normal. This is the best test to use under such circumstances. If the patient lives long enough and is not incontinent the 'phthalein elimination would give valuable additional data and the urea index will add information. For such a case the two-hour test is practically always inapplicable.

The following case will serve to illustrate how a comatose patient may show a considerable amount of albumen in the urine and have a high blood pressure when the condition is the result of cerebral haemorrhage rather than nephritis.

A negress of 32 (med. no. 5430) was brought to the hospital at 5 p.m. and from her friends the following story was obtained. Apparently she had been in good health until 1 o'clock when while waiting on the table she was taken suddenly with vomiting, fainted and became unable to talk. The vomiting soon ceased. No convulsions were observed in the patient and no signs of paralysis. Consciousness was regained shortly but inability to talk continued. When she got to the hospital she was semicomatose but could be slightly aroused and could speak though with difficulty. Her pupils were dilated and regular. A left divergent external strabismus was noted. In both fundi extensive fresh retinal haemorrhages were observed. Her heart was moderately enlarged; there were no murmurs; the rate was 64. The peripheral vessels were not sclerosed, the systolic blood pressure was 188; diastolic 118. The lungs and abdomen were negative. There were no signs of paralysis. The reflexes generally were decreased. The Kernig and Babinski signs were negative. Her neck was stiff. Lumbar puncture yielded bloody fluid. Repeated ophthalmoscopic examinations showed progressive increase in the size of the retinal haemorrhages. The blood pressure which on admission was 188 systolic in an hour had increased to over 300. Her urine showed a large trace of albumen (0.5 per cent) and a few red blood cells. There was also a definite trace of glucose. Her blood urea nitrogen was normal (10.95 mgm. per 100 cc. of blood). The patient died five hours after admission and autopsy revealed an extensive subdural haemorrhage from a ruptured small aneurysm of the left meningeal artery. The kidney in the gross appeared normal and microscopically there was no definite nephritis.

In another patient (med. no. 5895) there had been some blurring of vision and occasional headache for a year. One day at noontime he felt rather out of sorts and had a headache. This continued and about 10 p.m. he vomited. A physician saw him and noted that though the patient talked coherently it was with difficulty. The physician took a specimen of urine which next morning he reported as showing Bright's disease. During the following day the condition remained about the same and at 6 p.m. he was admitted to the hospital in a stuporous condition. He would respond to questions and said he had pain in his head. His pupils were regular and small. Ophthalmoscopic examination showed very slight blurring of the disc margins and some tortuosity of the arteries. His heart, lungs and abdomen were negative. He had marked Cheyne-Stoke's respiration. The blood pressure was 215 systolic; 120 diastolic. His peripheral arteries were slightly thickened and his pulse rate was 65. His urine showed a trace of albumen and a few hyaline casts. His blood urea nitrogen was not increased (18.2 mgm. per 100 cc. of blood). The next day his blood pressure rose to 270 and then fell gradually to 180, at about which level it remained for several days. His condition improved. Fifteen days after admission his condition became worse; his blood pressure increased to 240 and five days later he died. At autopsy extensive older haemorrhage was found in the right frontal lobe of the cerebrum and more recent haemorrhage in the left frontal lobe. The right sided haemorrhage occurred probably twenty days before death; the left sided one five. The kidneys showed a moderate degree of chronic interstitial nephritis.

In this last case the patient had been sent in to us as a case of uremia. Throughout his stay he had albumen and casts in his urine and a considerable degree of hypertension. His blood urea was not increased, and autopsy revealed extensive cerebral haemorrhage.

You might say that such a diagnosis was easy without renal functional tests. Perhaps so, but many such cases are actually sent to the hospital diagnosed as uremia and reading text books and systems of medicine I am inclined to think that many, though of course not all, cases there described as so-called sudden uremia not preceded by convulsions are not uremia at all. Anyhow I am skeptical enough to be unconvinced of the diagnosis of uremia in such cases unless postmortem examination has revealed both the absence of cerebral vascular lesions and the presence of extensive, not slight, renal lesions.

In cases in which the urine shows a slight albuminuria and cylindruria the diagnosis of slighter degrees of nephritis is much aided by functional tests. One of the early signs of renal insufficiency is shown by a tendency toward fixation of the specific gravity and percentage concentration of sodium chloride in the two-hour renal test, or by a gradual increase in the night amount of urine. Very often this is apparent when the elimination of 'phthalein is within or very near to normal figures and there is no increase in the blood nitrogen.

In these early cases of nephritis there is nearly always some evidence of disturbance in the kidney's selective excretory activity. That is, in one case the change in function is largely a disturbance in water excretion or total solids while in another sodium chloride or nitrogen excretion evidences greater disturbance. In still other patients all of these elements show about equal departures from the average normal type of excretion. Usually nitrogen elimination maintains a fairly normal curve of excretion after quite evident disturbance in the elimination of water, total solids and salt has taken place.

The following cases illustrate the type of disturbance shown by the two-hour test of renal function when the degree of nephritis is slight or only moderately advanced:

A patient of 36 (med. no. 1946) gave a history of dizziness and weakness in the left side seven weeks before admission. A little later on that day he had a severe attack of vomiting. This weakness at first increased and then gradually decreased. Seventeen days before admission he awoke one morning to find the right side of his face paralyzed. Physical examination showed essentially negative findings except for a blood pressure of 240 systolic; 206 diastolic, and hyperactive reflexes on the left side. Ophthalmoscopic examination showed essentially normal eye grounds. The 'phthalein test on November 25 showed an excretion of 49 per cent in two hours and a total nonprotein nitrogen in his blood of 28 mgm. per 100 cc. His two-hour test showed definite fixation in the specific gravity and the percentage concentration of sodium chloride (see fig. 1). There was also a slight increase in the night amount of urine. This patient died six months later from what was supposed to be pneumonia. Up to the time of this acute infection vascular hypertension, not nephritis, had been the disturbing factor.

A woman of 40 (med. no. 2218) gave a history of goiter beginning seven years before admission to the hospital with prominent symptoms of hyperthyroidism. For five years there had been the history of repeated attacks of bronchitis. For some time there had been shortness of breath and palpitation, also some oedema of the legs. Very

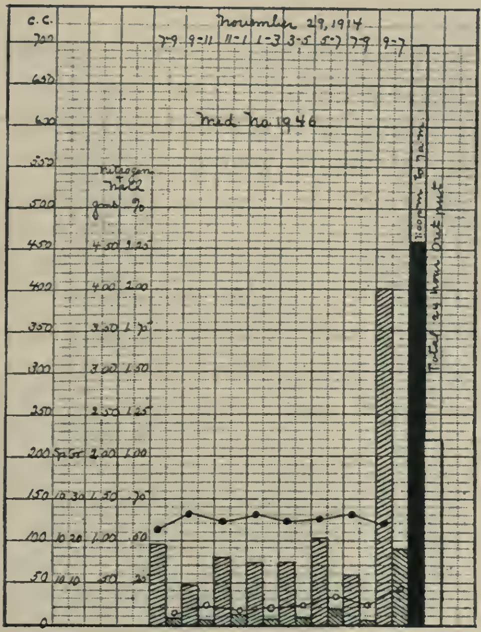

Fig. 1. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

recently there had been an acute attack of bronchitis. Physical examination showed signs of a diffuse bronchitis. The heart was enlarged and fibrillating. She had a systolic blood pressure of 175; diastolic 80. On February 18th the blood urea nitrogen was 19 mgm. per 100 cc. of blood. On February 23rd a phthalein test showed an excretion of 50 per cent in two hours. A two-hour renal test made on February 19 (see fig. 2) showed marked fixation of specific gravity and a moderate fixation of the percentage concentration of sodium chloride and nitrogen. The night amount was not increased. She had slight renal disturbance and definite cardiac decompensation.

A man of 67 (med. no. 2246) gave a history of polyuria dating back five years with occasional spells of dizziness. For the past few months

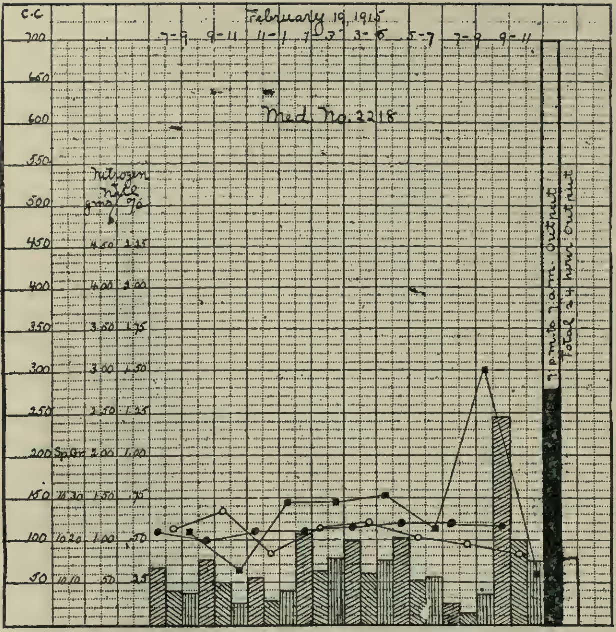

FIG. 2. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

there had been a slight tendency to shortness of breath. For five years he had been on a meat-free diet. Physical examination showed a moderately enlarged heart and a systolic blood pressure of 210; diastolic 90. Ophthalmoscopic examination was negative except for slight tortuosity and sclerosis of the retinal arteries. On January 31 the 'phthalein excretion for two hours was 21 per cent with a very small urinary excretion. On January 31st his urea nitrogen was 18 mgm. per 100 cc. of blood. The two-hour renal test (fig. 3) showed a small output of urine and solids with a rather fixed high specific gravity, but not much fixation in the percentage concentration of sodium chloride or nitrogen. The night amount was markedly increased. Here renal disturbance was greater than in the preceding cases.

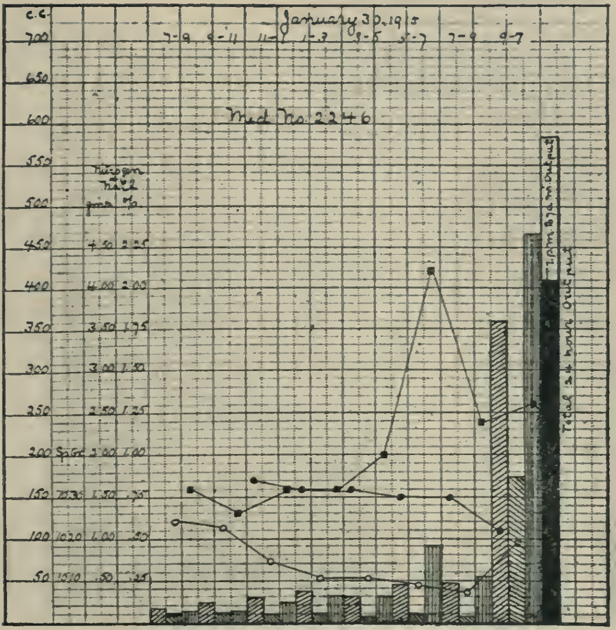

FIG. 3. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

A man of 52 (med. nos. 2357 and 2653) came to the hospital in February, 1915, complaining of shortness of breath and cough. For about a year he had been troubled with cough and shortness of breath with occasional attacks of nocturnal dyspnoea. Recently he had had orthopnoea. Physical examination showed moderate cardiac enlargement; a high pitched systolic murmur in the apex region; systolic blood pressure of 210 and diastolic 108. The lungs showed an emphysema and a chronic bronchitis. The eye grounds were essentially normal. On February 18th his 'phthalein output was 52 per cent. On February 19th his blood urea nitrogen was 18 mgm. per 100 cc. On March 2 his two-hour renal test (fig. 4) showed fixation in both

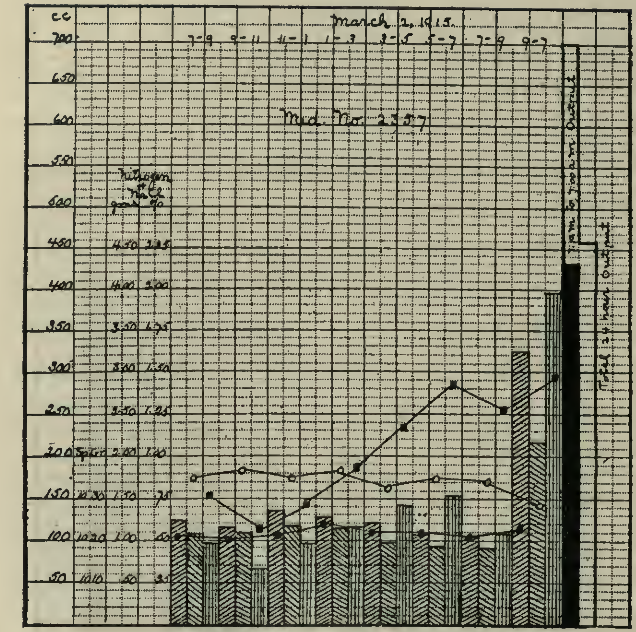

FIG. 4. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

specific gravity and the percentage concentration of sodium chloride. The night amount was essentially normal. On April 15, 1915, he came back to the hospital on account of a suddenly developing attack of weakness followed by headache and vomiting. Physical examination showed no change from the preceding admission. Here the disturbing factors did not arise primarily from decreased renal excretion.

In a man of 60 (med. no. 2428) there was a history of recent malaise, cough and shortness of breath. Physical examination showed a moderate cardiac enlargement; systolic bood pressure of 205 and diastolic 145. The 'phthalein excretion on March 14 was 61 per cent. The blood urea nitrogen on March 16 was 22.7 mgm. per 100 cc. of blood and a two-hour renal test (fig. 5) on March 16 showed pretty marked fixation in specific gravity without fixation in the percentage concentration curves of sodium chloride and nitrogen. The night amount of urine was normal.

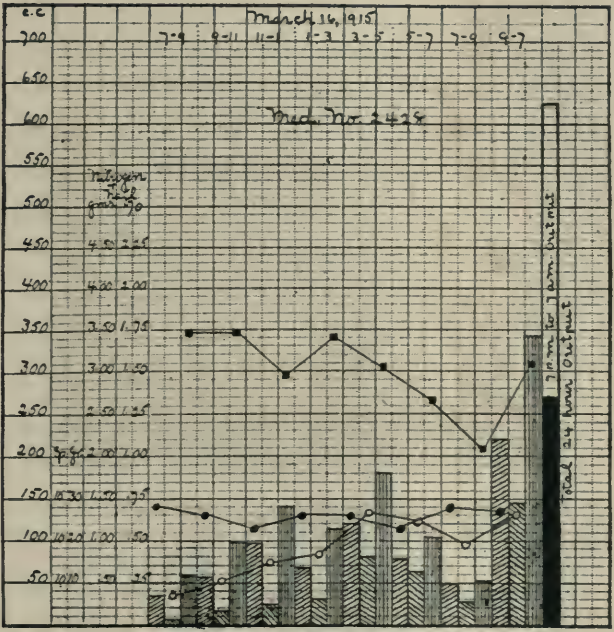

FIG. 5. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

In a woman of 41 (med. no. 2473) there was a urine which occasionally showed traces of albumen and a few hyaline casts. Her blood pressure was 180, phthalein excretion 55 per cent in two hours, and blood urea nitrogen 9.7 mgm. per 100 cc. of blood. The two-hour renal test (fig. 6) gave very slight fixation in the specific gravity, slightly more in the percentage concentration of sodium chloride and none

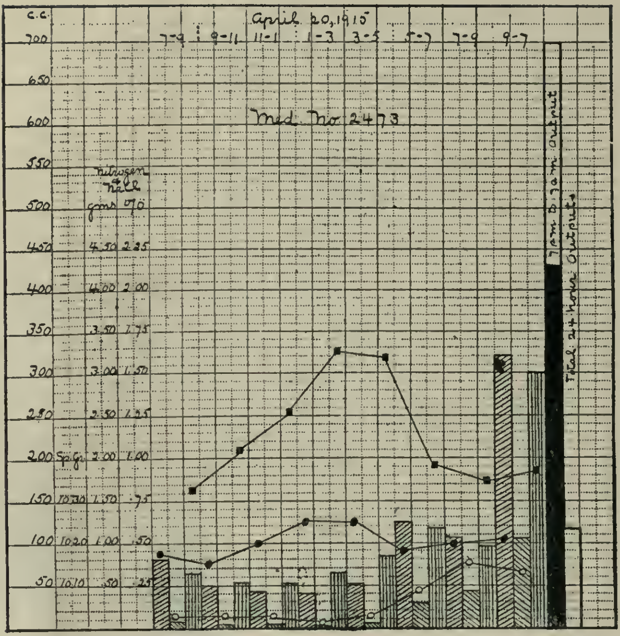

FIG. 6. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

in the nitrogen. The night amount of urine was proportionately moderately increased. A year later this patient reported that she felt essentially well.

This fixation in the curves of excretion, however, cannot be considered in itself an evidence of nephritis. I have found very similar curves of excretion in cases of pernicious anaemia with normal kidneys. In a typical case of pernicious anaemia (med. no. 4181) in a man of 51, when the haemoglobin was 43 per cent and the red blood cells 2,000,170 the two-hour renal test on April 11 (fig. 7) showed marked fixation in the specific gravity

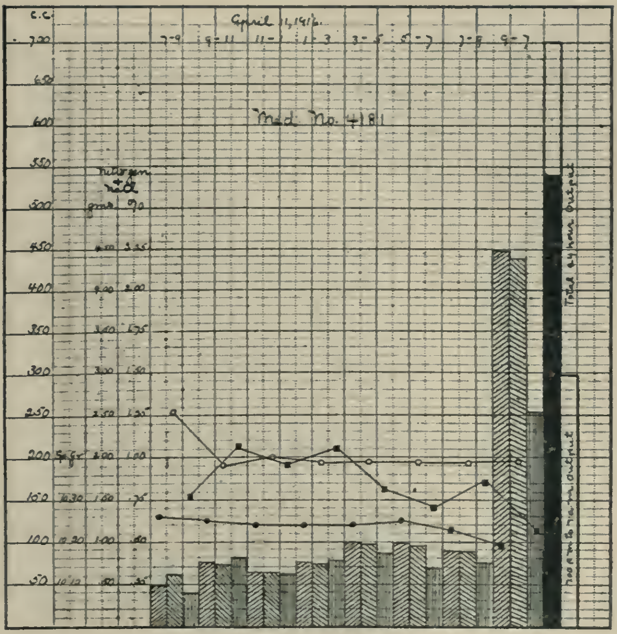

FIG. 7. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

and the percentage concentration of sodium chloride, and an increased night amount; whereas on May 3, with a haemoglobin of 82 per cent and a red blood cell count of 3,500,000 there was much less fixation in both curves (fig. 8) but still the increased night amount of urine persisted.

These same changes also occur in cases of cardiac decompensation where chronic passive congestion of the kidney exists rather than nephritis. In a typical case of mitral stenosis with auricular fibrillation in a man of 33 (med. no. 1683) there was a 'phthalein excretion of 43 per cent in two hours. The two-

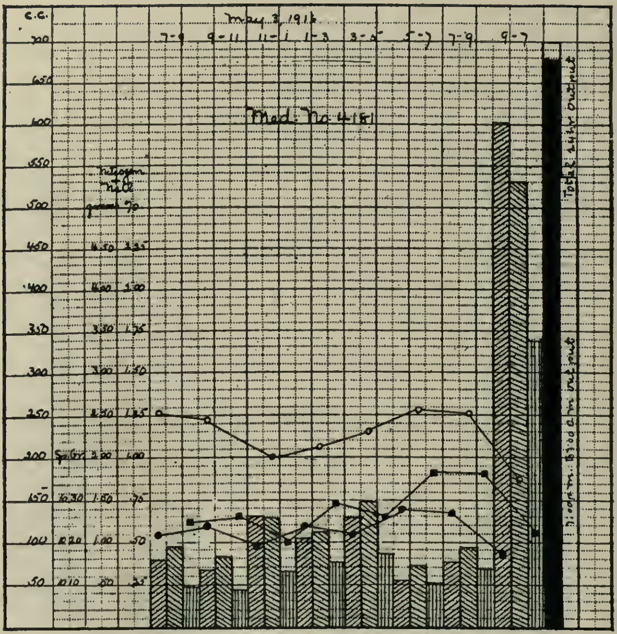

FIG. 8. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

hour renal test (fig. 9) showed a marked fixation of the specific gravity at a high level and also a fixation of the percentage concentration of sodium chloride at a low level.

The two-hour renal test when it shows a departure from the normal average type of curve indicates a disturbance of renal function. Whether this disturbance is indicative of nephritis depends on a consideration of other factors in the case. Again let me emphasize the importance of not placing too great reliance on any single method of studying a patient.

In some early cases of nephritis there is an increased elimina-

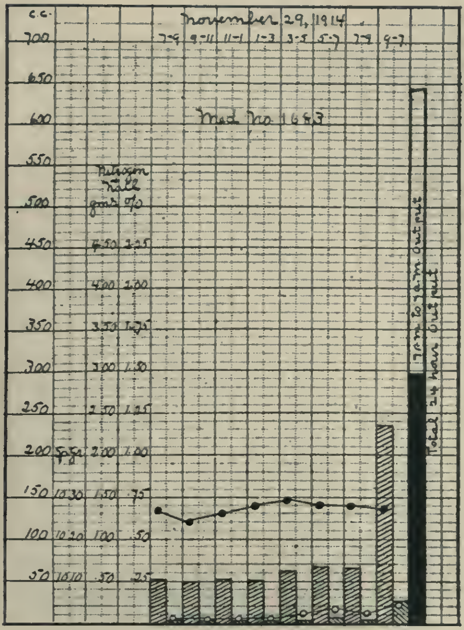

FIG. 9. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

tion of water, salt and nitrogen in the earlier periods of the day and this renal hyperirritability signifies a slight degree of renal damage. This is well shown in a man of 65 (med. no. 2237) with a normal blood pressure and a 'phthalein excretion of 60 per cent in two hours (see fig. 10).

Sometimes in patients with more marked evidence of nephritis this same morning hyperirritability is shown. This is illustrated by a man of 35 (med. no. 2132) with a systolic blood pressure of 240, a 'phthalein excretion of 33 per cent in two hours, and a blood urea nitrogen of 29 mgm. per 100 cc. of blood (see fig. 11).

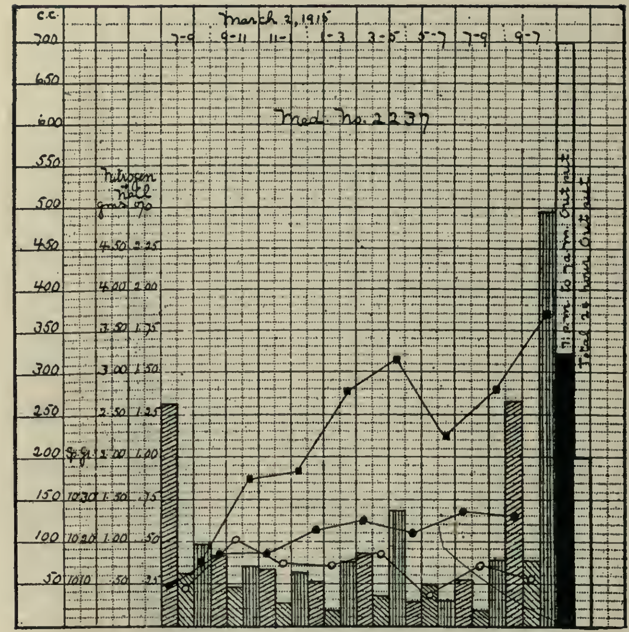

Fig. 10. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

In the very early stages of renal lesion the rate of urea excretion is increased and the index of excretion is high, often far above the normal of 80 to 120. This is illustrated by a boy of 15 (med. no. 2444) who had albumen in his urine, no casts, a 'phthalein excretion of 62 per cent a blood urea nitrogen of 10 mgm. per 100 cc. of blood, pretty normal curve of excretion in his two-hour renal test (fig. 12) and a normal night amount of urine, but who had an index excretion of 605 per cent. This is also illustrated by a second patient, a woman of 33 (med. no. 2548), in whom there was a slight increase in blood pressure.

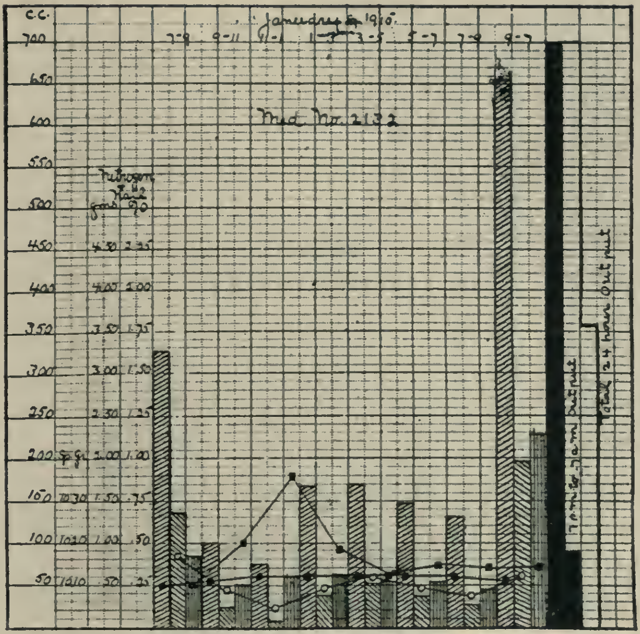

FIG. 11. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

Her urine contained a very slight trace of albumen and an occasional cast. There was a 'phthalein excretion of 65 per cent, a blood urea nitrogen of 9.4 mgm. per 100 cc. of blood and a two-hour renal test (fig. 13) showing no abnormality in the curves. She had an index of excretion of 215 per cent.

An index of urea excretion above normal, however, is not pathognomonic of nephritis. Such high indices are found in other conditions such as fevers or in hyperthyroidism. In the latter especially is it very likely that the high index is a part of the increased rate or metabolism which we find in patients with hyperthyroidism.

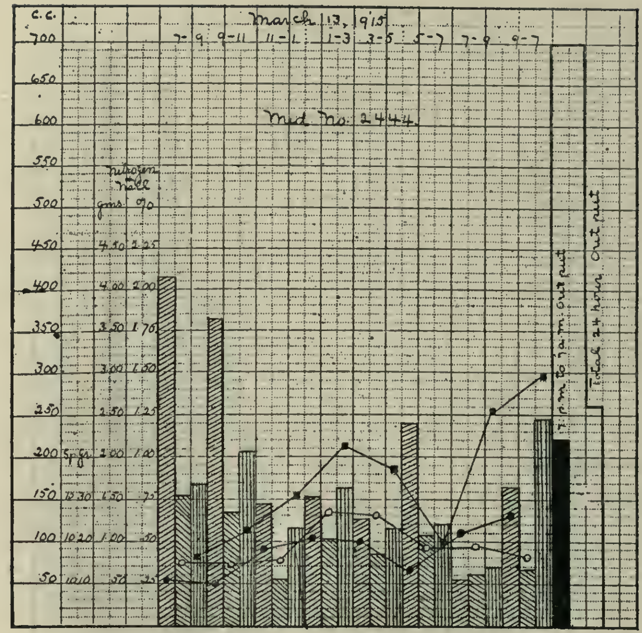

FIG. 12. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

A little later in an early renal involvement the rate or urea excretion decreases and the index falls below normal, though the amount of blood urea may be even less than the average normal. In such a case where the index is high and then gradually falls below normal there is a stage when the index for a time is normal and yet it is obvious that the kidney is damaged. In the later stages of nephritis the index is quite low. The determination of the index of urea excretion often is of diagnostic aid in cases of nephritis; both high and low indices indicate renal disturbance, but like other tests, they are not necessarily pathognomonic of nephritis.

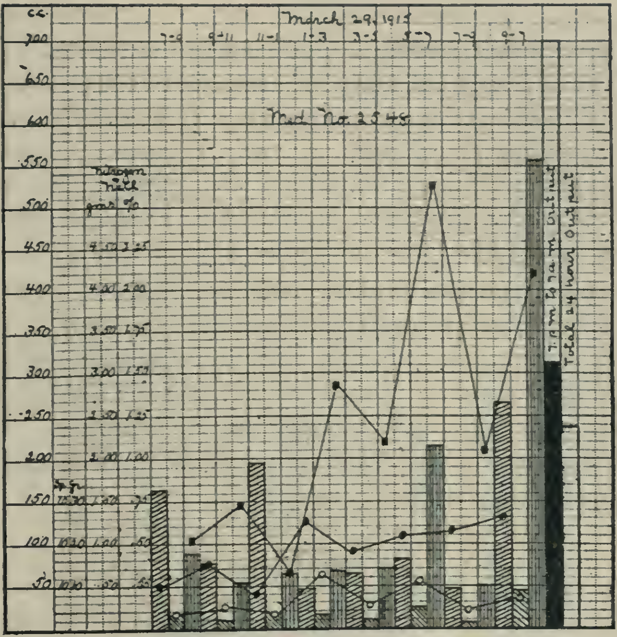

FIG. 13. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

Not infrequently in cardio-renal cases it is not evident whether the nephritis or the cardiac and renal circulatory disturbance is the important causative factor of the oedema. In such patients the urine is rich in albumen and casts, the 'phthalein output is decreased and the index of urea excretion is lowered. In such cases the diuretic response to drugs such as digitalis and theocin is a good test of renal function. Where a prompt diuresis can be produced this is good evidence of a kidney structurally and functionally fairly intact provided chronic passive congestion can be decreased by proper cardiac therapeusis.

In a man of 61 (med. no. 3737) with the physical signs of a chronic myocarditis, with a blood urea nitrogen of 22.7 mgm. per 100 cc. of blood, an index of urea excretion of 19.9 per cent and a 'phthalein excretion of 30 per cent in two hours, theocin produced a prompt diuresis; on one occasion increasing the twenty-four hour amount from 300 to 11,220 cc. and on another occasion from 500 to 3900, pretty good evidence that he had but slight nephritis.

Another patient a man of 42 (med. no. 2212) who was a typical case of aortic stenosis and insufficiency, who had a 'phthalein output of only 12 per cent in two hours showed with theocin and digitalis a diuresis, increasing the urinary output from 600 to 3500 cc. and from 900 to 4400 cc. as examples. Sometime later this patient died and his kidneys except for chronic passive congestion were essentially normal.

PROGNOSIS

In prognosis these tests of renal function are of more practical help than in diagnosis. All four of the tests enumerated aid in prognosis. The two-hour test, however, is not of very great service in more advanced cases for as the lesion in the kidney progresses the stage of pretty complete excretory fixation is soon reached and beyond this there is relatively little change as the nephritis advances. When the two-hour renal test gives evidences of well maintained concentrative ability prognosis is good. When the nephritis progresses the curves gradually flatten out and the flattened curves indicate a renal lesion that has progressed beyond the early stages.

This is quite well shown by one of our patients a young woman of 28 (med. no. 4010) who had had practically no symptoms of nephritis. All her life she had had frequent sick headaches. There had been no visual disturbance suggestive of nephritis. Two years ago she felt run down and her physician found urinary evidence of nephritis. When seen by us her physical examination was essentially negative except for a slight increase in blood pressure, 140 systolic, 100 diastolic. Her urine had a low specific gravity, 1007; a moderate trace of albumen and a very occasional cast. 'Phthalein elimination was 38 per cent in two hours and her blood urea nitrogen was 45.6 mgm. per 100 cc. of blood with an index of urea excretion of 17.1 per cent. A two-hour renal test on January 23 showed (fig. 14)

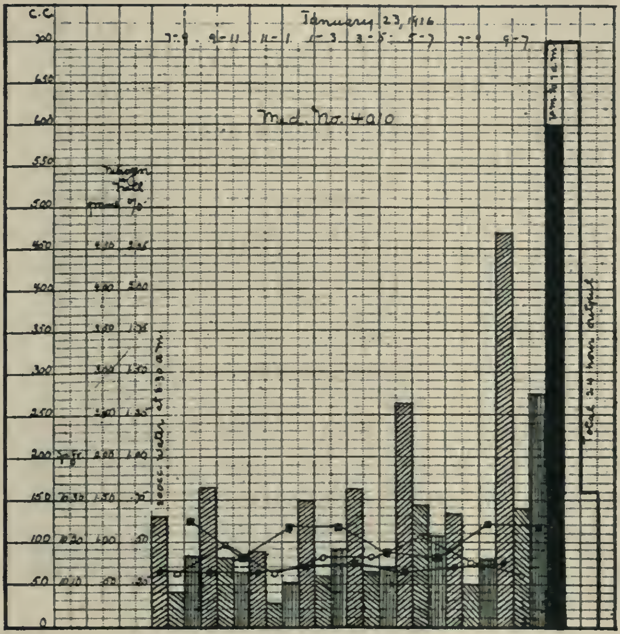

Fig. 14. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride and nitrogen in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of urine and the percentage concentration of sodium chloride and nitrogen in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

marked fixation in the curve of specific gravity, slight fixation in the curve of percentage concentration of sodium chloride and of nitrogen, and an increased night amount of urine. In May a repeated two-hour renal test showed no change. In November of the same year the test (fig. 15) showed progression in the lesion by the curve of percentage concentration of sodium chloride becoming flattened out like the earlier curves of specific gravity and the night amount of urine was still more increased.

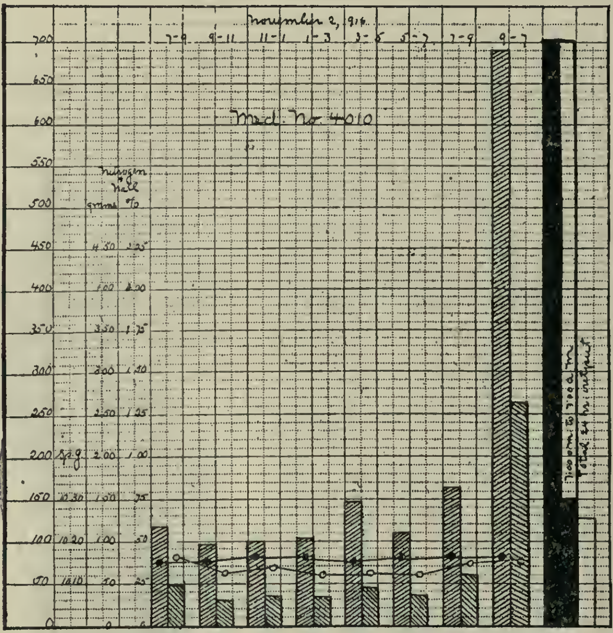

FIG. 15. The series of columns beginning at the left give the amount of urine in cubic centimeters and sodium chloride in grams in each two hour portion of urine from 7 a.m. to 9 p.m. and in the portion from 9 p.m. to 7 a.m. The solid lines joining the dots in the space of each column give the variations in the specific gravity of the urine and the percentage concentration of sodium chloride in each portion of urine. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

Also the amount of urine and amount of sodium chloride in each two-hour portion in this last test showed less variation than in the first. During this period her blood pressure had not increased. Here we are dealing with a slowly progressing nephritis which so far has caused no very serious symptomatic disturbance and yet the renal lesion has progressed further than the general condition indicates. The two-hour renal test will be of little more help in this case for already the nephritis is far enough advanced to give flattened curves of excretion with pretty uniform concentration and amounts from two-hour period to two-hour period throughout the day. The other tests of renal function need to be used in following her further progress.

In more advanced cases the 'phthalein output, the rate of nitrogen excretion and its accumulation in the blood and the diuretic response to such a drug as theocin are of the greatest help in estimating the severity of the renal lesion. In forming any idea of prognosis, however, it is important to repeat the tests after an interval to see whether the renal lesion has progressed much in this period of time. As many of these tests give a numerical value to renal function, comparison of successive tests becomes easy. Here again it is necessary to interpret the results in connection with other changes in the patient and to exclude a number of extraneous effects that might lead to misinterpretation of renal tests.

In some cases of nephritis the advance of the lesion is a steady progressive one. A group of tests compared with a second group repeated after an interval enables us to judge of the probable duration of life provided intercurrent infections do not lead to acute exacerbations of the nephritis. It is particularly in the type of nephritis with little albumen, few casts, little or no oedema and high blood pressure, that is the type of a chronic interstitial lesion, that this is apt to occur. With them tests of renal function give a pretty accurate measure of renal lesion.

In other cases progression is not steady but by irregular exacerbations. This seems more prone to occur in nephritis with much albumen, many casts, much oedema and slight increase in blood pressure, the type of a chronic parenchymatous nephritis. Here prognosis is far more uncertain. Furthermore in this group functional tests give less accurate measure of renal damage. Abnormal renal permeability appears to combine with defective elimination to give higher excretory values than the extent of the renal lesion seems to justify. With them the two-hour test sometimes gives more evidence of renal lesion than do 'phthalein elimination and the urea content of the blood or index of urea excretion. In this group, though functional tests give only moderately depressed figures, we have learned to set a relatively poorer prognosis for such cases.

The differences in these two general groups justify my previous remark as to the folly of attempting interpretation of test of renal function without good knowledge of the patient's condition as measured in other ways than by tests of renal function.

Another fact must always be kept in mind in rendering a prognosis. The tests we are describing are tests of renal function; they justify only a prognosis in so far as renal efficiency is concerned. We can say in a given case renal function is fair and is decreasing slowly; with regard to the kidney prognosis is good. That patient may have a very high blood pressure and already show evidences of myocardial damage or of arterial lesions, so we must give a relatively poor prognosis with regard to length of life because the probability of cerebral haemorrhage or cardiac failure is great. Particularly the cerebral haemorrhage may occur at any time and cut short the individual's life. In a sense such is an accident and unpredictable, but with signs of arterial degeneration it becomes increasingly probable.

This is quite well illustrated by a man of 53 (med. no 1340) who came to the hospital in June, 1914, on account of profuse nose bleed. At that time his blood pressure was 225; he had a 'phthalein excretion of 38 per cent in two hours and a total non-protein nitrogen in his blood of 35.2 mgm. per 100 cc. The nose bleed was stopped by cauterization. Examination of the fundus of his eyes showed one small haemorrhage and arteries that were small and tortuous and the arteries showed a marked light streak. He left the hospital in good condition. His renal prognosis was regarded as relatively good. In June, 1915, his physician reported that he was in the best of health. In December, 1916, he developed a headache, rapidly became unconscious and died in a short time. Autopsy showed an extensive cerebral haemorrhage with only moderate changes in his kidney.

In another hypertension patient with evidences of good general nutrition and viscera functioning well, including the kidney, a far better prognosis should be given. A most excellent example of this is in a man of 53 (med. no. 1955) who was seen in November, 1914, because his blood pressure had been found to be high and he had recently developed a chorioretinitis. He was a vigorous, active man who had had no symptoms. He had been in the habit once or twice a week of going in swimming throughout the Winter and of walking fifteen to twenty miles a day. He had been temperate in his habits. At this time

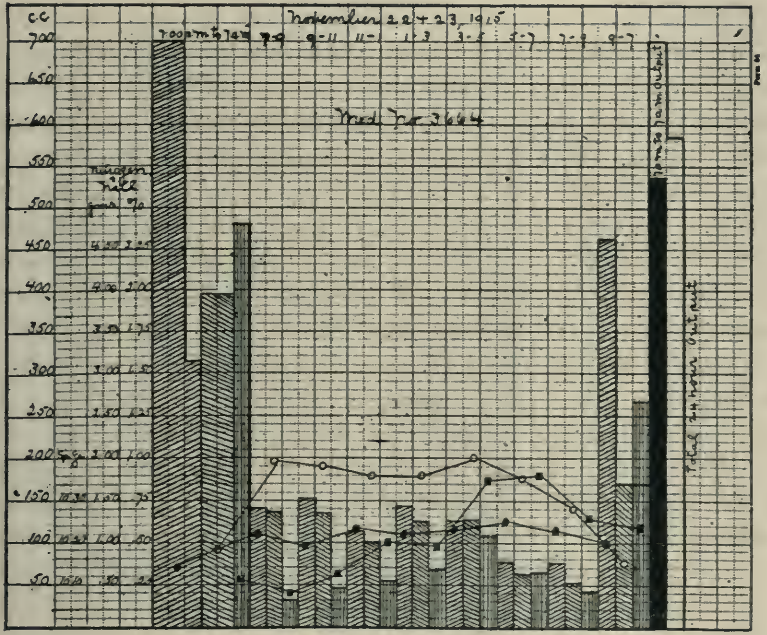

FIG. 16. The series of three columns beginning at the left refer to the urine portion collected from 7 p.m. to 7 a.m. The next series of columns give the results of the analysis of the urine collected in separate portions throughout the day, and the next succeeding night. In both of these the columns give the amount of urine in cubic centimeters and the sodium chloride and nitrogen in grams in the different portions of urine. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in these several portions. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

he had a systolic blood pressure of 190, a 'phthalein excretion of 60 per cent in two hours; total non-protein nitrogen in his blood of 24.5 mgm. per 100 cc. and he had a urine that showed no albumin and very rare hyaline casts. A year later (med. no. 3664) his blood pressure was systolic 225; diastolic 100. His 'phthalein excretion was 58 per cent in two hours. His blood urea nitrogen was 14.2 mgm. per 100 cc. with an index of urea excretion of 125 per cent and a two-hour renal test (fig. 16)

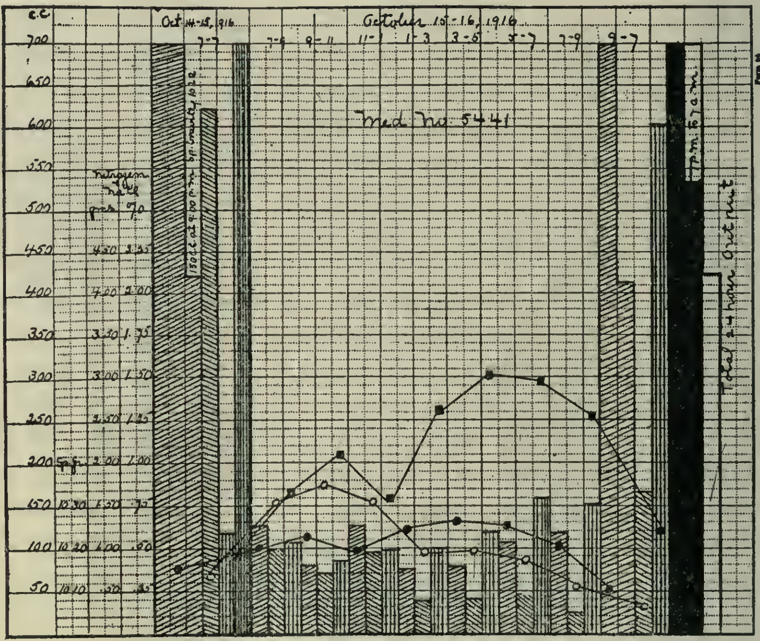

FIG. 17. The series of three columns beginning at the left refer to the urine portion collected from 7 p.m. to 7 a.m. The next series of columns give the results of the analysis of the urine collected in separate portions throughout the day, and the next succeeding night. In both of these the columns give the amount of urine in cubic centimeters and the sodium chloride and nitrogen in grams in the different portions of urine. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen in these several portions. The solid black column on the right indicates the night portion of urine, while the column enclosed by the lines at the same point, indicates the total twenty-four hour amount of urine in cubic centimeters.

which showed a very moderate degree of fixation in the specific gravity and other curves, and a moderate increase in the night amount of urine. A year later, October, 1916, (med. no. 5441) his blood pressure was sytolic 222, diastolic 102. His urine showed no albumen; no casts. His 'phthalein excretion was 37 per cent in two hours. His blood urea nitrogen was 19.5 mgm. per 100 cc. of blood. His index of urea excretion was 77.5 per cent. His two-hour test was normal as in the year before (fig. 17), except for a greater increase in the night amount of urine. He still is vigorous and apparently in the best of health, although his tests show a slight progression in his renal lesion.

When all is done and said even from careful tests of renal function in patients thoroughly studied by modern methods, numerous errors in prognosis are still inevitable. The patient whose lease of life seems at best a short one appears a year later in just as good condition, possibly better, than when he left you and perhaps a year later again he reappears. Just why he has not progressed as predicted you do not know. For some unexplained reason his renal disease has become stationary. Another patient in just the opposite way fools you, your good prognosis is a mistake; the mild renal lesion progresses at an extraordinary rate and your patient dies a renal death long before you had anticipated. However, such cases do not make up a very large per cent of renal cases. More often the disease progresses as predicted and your prognosis based on renal functional tests and other data is correct.

TREATMENT

Tests of renal function may aid in treatment in several ways. In so far as they measure the extent and severity of the renal lesion they serve as a guide to the amount of limitation that should be placed on the bodily activities of the patient. They help in determining such a question as to the advisability of permitting pregnancy to take place in one who has albuminuria, pregnancy becoming increasingly undesirable as evidences of decreased renal efficiency appear more and more evident from our tests. They may be of much use in guiding us as to advice to give a patient with regard to undertaking business ventures, etc.

Tests of renal function serve as guides to dietary limitations for patients. It seems rational to place stricter limitations on sodium chloride intake in patients whose functional tests show a markedly decreased sodium chloride elimination. The same applies to proteid restrictions in patients with poor nitrogen elimination and those in whom nitrogen accumulation in the blood is taking place. Where the elimination of these substances is reasonably good, there is a distinct advantage in a more liberal diet. In this phase of the problem our practical knowledge is limited for very little good observation over fairly long periods is available as a basis of determining the value of the tests in these respects.

A knowledge of renal function is particularly useful in patients with high blood pressure; when renal function is reasonably good and there are few if any signs of cardiac deterioration patients of this type should have only slight restrictions. In such cases too strict limitations seen to be directly harmful. On the other hand when renal damage is quite marked prompt restriction in diet and in activity is very important and when carried out prolongs life.

Renal function should serve as a guide to the use of diuretics in patients with oedema. When renal function is poor diuretics are contra-indicated because they seem definitely to cause a still further lowering of renal function. In such cases they produce no diuresis and to increase dosage simply decreases renal function further. In less advanced renal lesions diuretics produce a diuresis, but if continued too long the diuretic effect is lost because even in patients in whom a diuresis is produced the diuresis is followed by a lowered renal function. Here an intermittent use of diuretics is indicated.

High figures for blood nitrogen in nephritics serve as a good index for active elimination by sweating and purging and for bleeding. With the last frequently very striking improvement may be obtained if bleeding is not postponed too long. Repetition of the tests indicate the efficacy of eliminative treatment.

So far remedial measures appear to have received less attention in relation to tests for renal function than have diagnosis and prognosis. Particularly do we lack observations on the effect of restricted diets or forced fluids, etc., maintained over longer periods of time in which period tests of renal function are made as measures of efficacy of treatment. We assume that it is advantageous to limit proteid intake in the patient with advanced nephritis; we often observe striking progress in symptoms when dietary limits are transgressed, but we have little real knowledge of the recuperative power of the kidney or its ability to re-establish tolerance if rested by a restricted diet, the principle which now governs our dietary regime for diabetics. There seems to be need for much careful investigation along these lines.

Tests for renal function are reasonably simple. The general practitioner naturally sees the nephritic from his early stages to the late; the family physician if he choses to learn and to apply tests of renal function is in the best position to work on the problem how most satisfactorily to manage the nephritic by dietary and other methods. The consultant and hospital physician can do less with this problem for he but rarely can follow his patients over the long periods of time which represent the life history of many chronic renal lesions. The careful method of study that Mackenzie carried out as a country practitioner in England with his cardiac cases followed for periods of fifteen to twenty years added more new light on heart disease than had come in the same period from hospital and laboratory study. Just such a sort of investigation is needed for nephritics; furthermore it is possible to carry out such studies. The tests of renal function which I have enumerated above are no whit more difficult than the polygraphic methods which Mackenzie used, in fact, devised for his heart cases. Here lies in my judgement a profitable field of investigation for the general practitioner of medicine. To use tests of renal function in your patients with nephritis will, I am sure, materially aid you in their care.

Peter Bent Brigham Hospital.

SEVERE RENAL INSUFFICIENCY ASSOCIATED WITH ATTACKS OF URTICARIA IN HYPERSENSITIVE INDIVIDUALS

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Following an observation by one of us (1) that repeated anaphylactic shock in rabbits, dogs, cats, and guinea-pigs frequently results in an injury to the cells of the kidney, a series of twelve cases of serum disease in man was investigated by Rackemann, Longcope and Peters (2) to determine whether there was any injury to the kidney during this illness which might be determined through a study of certain renal functions. Under the conditions of the observations, no constant or significant changes were found in the blood urea, or urea excretion, and in only two cases was the excretion of phthalein reduced during the serum sickness. There was, however, a profound though transient impairment in the excretion of chlorides and water. This was thought to be a direct result of the intoxication in serum disease and was associated with subcutaneous oedema. This chloride and water retention seemed to be due in part to direct injury to the body tissues and in part to impairment of kidney function.

We have shown, however, that the reaction of the skin and mucous membranes is much more violent in the spontaneously sensitive than in the artificially sensitized and it, therefore, seemed of importance to repeat similar observations upon patients belonging to the latter group. In these patients the tissue reaction to repeated intoxications may be very marked. This is especially noticeable in chronic eczema which Blackfan (3) has shown is often associated with hypersensitiveness to some food protein. In this condition an actual chronic inflammation of the skin exists, and the hyperplasia of the lymph nodes may be excessive. Repeated attacks of asthma may lead to a chronic bronchitis and it is not inconceivable that repeated injuries to the kidney or liver may lead to chronic alteration in these organs. But since all the tissues are not equally affected in the spontaneously sensitized individuals, one group presenting symptoms referable to the skin, another to the respiratory tract and still others to the gastrointestinal tract, we could only expect the internal organs to be affected in a comparatively small percentage of instances.

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[1] Coolidge Fellow in Medicine.

We have chosen for study cases that manifested such cutaneous lesions as urticaria, erythema multiforme and eczema. In these individuals the foreign protein, if it is the cause of the condition, probably produces its effect after absorption from the gastrointestinal tract and may, on this account, come in contact with the various tissues of the body.

The actual frequency with which one can demonstrate that these skin affections are associated with hypersensitiveness to foreign protein varies. In a group of seventeen cases that we have previously studied, twelve of which suffered from urticaria, one from angioneurotic oedema, one from eczema and three from a combination of urticaria and mild purpura, eight or 47 per cent gave a positive skin reaction to one or more foreign proteins. The methods employed in performing these reactions is described elsewhere (4). The proteins used for making these tests was the blood serum of the horse, sheep, beef, pig, dog, cat, hen, and duck; egg white, cow's milk, casein; extracts of crab meat, oysters and clams; phaseolin and glutelin, extracts of barley, oats, wheat, strawberries, ragweed, goldenrod and redtop.[2] The skin reaction was positive in one case to beef and sheep serum, in one to beef and pig serum; in one to beef juice and eggwhite; in one to beef serum and phaseolin; in one to horse, sheep, beef, pig serum and crab extract; in one to milk and rabbit serum; in one to beef serum, redtop and strawberry extract, and in one to crab, oyster and clam.

The present study includes four of these positive cases, one negative case and one case of erythema multiforme in which skin reactions were not made. The methods employed to study the renal functions were the following: the total twenty-four hour fluid intake and twenty-four hour urine output, as well as the chloride intake and excretion were measured daily; the phthalein excretion was determined, the blood urea and urea index measured by the McLean formula, and in one case the plasma chlorides studied. The abstracts of the histories of these six cases are as follows:

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[2] For the vegetable proteins we are indebted to Dr. T. B. Osborne and Dr. H. G. Wells; for the pollen extracts to Dr. Robert A. Cooke of New York.

Case 1. Mrs. I., age 30, was admitted to the Presbyterian Hospital, September 12, 1916, with a complaint of hives and irregular red swellings of the skin. Fifteen years previously she had had hives with swollen face which lasted over a period of two years and appeared during this time in daily attacks. From then until the present time she had been perfectly well. During the summer she was camping in the woods where the variety of food was fairly limited. One month ago while at camp she developed severe hives which have persisted ever since. Physical examination showed nothing abnormal except the condition of the skin. Throughout the day and night, irregular red itching urticarial wheals appeared over the body. Together with this there were larger white swellings which appeared about the lips and over the legs. Blood pressure: Systolic, 110; diastolic, 68. September 14: Hemoglobin, 90 per cent; leucocytes, 6600; polynuclears, 67 per cent; small lymphocytes, 30 per cent; large mononuclear cells, 3 per cent. Urine: Specific gravity, 1030; straw colored; no albumen; no sugar. Microscopic examination: epithelial cells and leucocytes.

September 22: Phthalein, 63 per cent; blood urea, 15 mgm. per 100 cc. Urea index excretion, 126. Patient gave positive skin reaction to phaseolin and beef serum. Beef and beans removed from diet with rapid relief from urticaria.

Case 2. E. D., female, unmarried, age 29. Admitted to the Presbyterian Hospital June 1, 1916, with a complaint of hives and swelling of the face. History was unimportant except that she had had several attacks of tonsillitis. For two months she had had recurring daily attacks of large white soft swellings on the face, lips, eyes and various portions of the body, varying from the size of a walnut to an orange. Physical examination showed no abnormality except for these repeated attacks of angioneurotic oedema. The blood pressure was rather low—systolic, 90; diastolic, 64.

September 11: Phthalein, 65 per cent; blood urea, 10 mgm. per 100 cc.; urea index, 61 per cent. Sodium chloride was excreted normally on a fixed intake, and an addition of 9 extra grams to the diet was eliminated within thirty-six hours. Urine: Specific gravity, 1012–1022; clear; no albumen; no sugar; no casts. Skin tests gave no positive reactions. Cause of angioneurotic oedema undetermined.

Case 3. W. G. S., male, age 27, single. Admitted to the Presbyterian Hospital November 13, 1916, with a complaint of eczema which he has had since the age of two months. His maternal grandfather was always violently poisoned after eating egg. Mother gave no history of any definite susceptibility. Since the age of two years has had several violent attacks of urticaria, once after eating an egg, and once after eating oysters. Has had swelling of the mouth, tongue, and lips after eating walnuts and fresh meat. Eczema constantly since the age of two years. Physical examination showed an extensive eczema, dermatitis, and thickening of the skin over the entire body with marked enlargement of all the superficial lymph nodes. Except for these, the physical examination showed nothing abnormal. Urine: Specific gravity, 1022; no albumen; no sugar; microscopic examination, negative. On fixed chloride and water intake, excretion of chloride and water was normal.

November 14: Phthalein, 40 per cent; blood urea, 20 mgm. per 100 cc.; urea index, 130.

November 16: Phthalein, 55 per cent. Plasma chloride, 5.85 grams per liter. Marked skin reaction to eggwhite and beef juice.

Case 4. Dr. S., age 32. Admitted to the Presbyterian Hospital, March 4, 1915, with a complaint of albuminuria, and casts in the urine of four months' duration. He had scarlet fever and diphtheria at the age of eight. In May, 1909, he had an acute frontal sinusitis. Since that time he has had two mild attacks of sinusitis at intervals of two years. Numerous attacks of asthma, and of urticaria and asthma after eating beans. In February 1915, cellulitis in the right foot, from which he recovered rapidly. In September 1915, he tasted by mistake a small amount of meal which contained pulverized beans. Immediately afterwards his face became swollen, he had a severe attack of asthma, and then a generalized eruption of urticarial wheals. This lasted for several hours but then rapidly subsided and he was quite well the next day. Shortly after this attack in November, he experienced headaches for several days. He then examined his urine, and found for the first time that it contained large quantities of albumen. He came to the hospital for general investigation. The general examination showed nothing abnormal except for the albumen and casts in the urine. The specific gravity averaged 1024. There were constantly moderate amounts of albumen and hyaline and granular casts. Blood pressure: Systolic, 128; diastolic, 96. Examination of the prostate showed nothing abnormal. Examination of the facial sinuses by Dr. Coakley, showed them to be normal. Eye grounds showed nothing abnormal.

March 6: Phthalein, 52.5 per cent; blood urea, 17 mgm. per 100 cc.; urea index, 102. The water and chloride exchange were normal. Skin tests gave positive reaction to phaseolin, redtop, goldenrod, ragweed, timothy, and strawberries. Reaction to all other substances negative.

Case 5. H. D. J., a man 45 years of age, English, married, was admitted to the Presbyterian Hospital June 25, 1916, complaining of hives. He had two children, one of whom had had similar trouble. Except for frequent colds and the attacks of urticaria, he had always been well. The attacks of urticaria started twelve years ago. At first he had one attack a year at no regular season. After two or three years they recurred two or three times a year. Now he has at least three attacks a year which last from thirty-six to forty-eight hours, and on three occasions recently they have been followed by recurrences at five to seven day intervals. He described the attacks as follows: at first there was itching of the tongue and lips together with an acute coryza. This was followed by swelling of the lips, throat and face. At the onset there was slight fever. Within a few hours there was nausea and vomiting which lasted twelve to twenty-four hours. The face and eyes continued swollen. About twelve hours after the onset a profuse and extensive giant urticaria appeared all over the body. There were no joint pains. Gradually the symptoms subsided and the patient was well but weak at the end of two or three days. He knew of nothing that precipitated the attacks. On admission he was in the midst of such an attack. The eyes and face were swollen. The body was covered with an urticarial eruption, which involved the mucous membrane of the mouth. There was no enlargement of lymph nodes. The general physical examination showed no other abnormalities. The leucocyte count was 10,100 with 81 per cent polymorphonuclears, and 19 per cent small lymphocytes. The Wassermann reaction was negative. The blood urea was 98 mgm. per 100 cc.; the index of excretion, 5.47; the phthalein, 18 per cent; and large quantities of albumen and casts were present in the urine. Four days later, on June 30, the patient had recovered. At this time the blood urea had fallen to 49 mgm. per 100 cc., the index of excretion risen to 62 and the phthalein excretion to 37. After leaving the hospital, three remissions occurred, the first July 4, the second July 10, the third July 15. He returned to the hospital in September, 1916, for further investigation. He was placed on a fixed diet containing 60 grams of protein much of which was in the form of beef. Three days after admission the patient suddenly developed an attack of urticaria similar to the one just described (fig. 1). We were fortunate enough to observe the patient through this attack. With the onset of his symp-

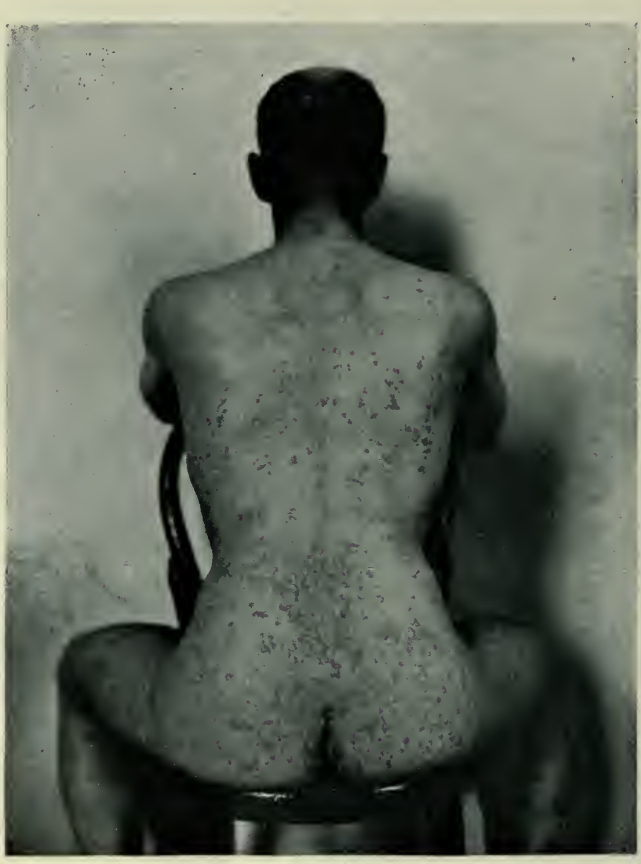

Fig. 1 Case V

Distribution and extent of eruption during acute attack of urticaria

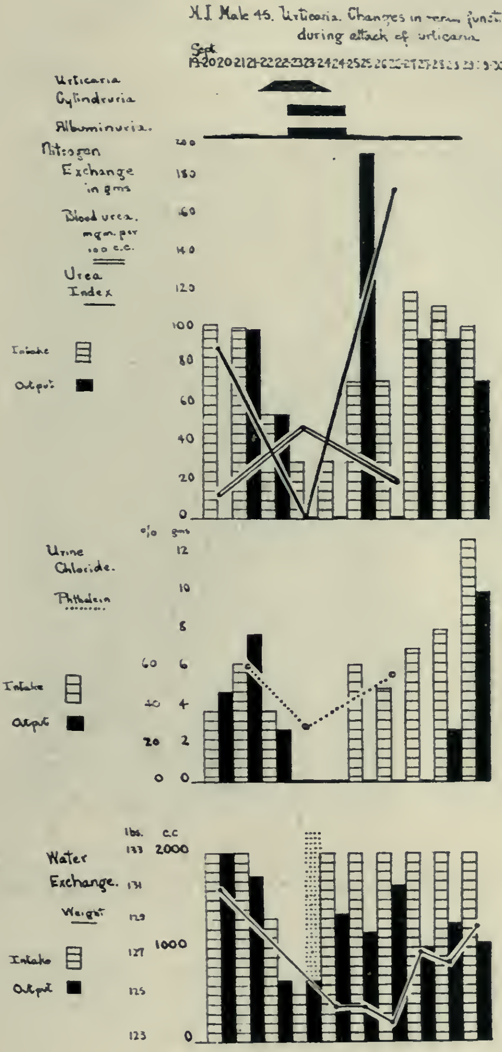
H.I. Male 45. Urticaria. Changes in renal function during attack of urticaria
Sept
19-20 20-21 21-22 22-23 23-24 24-25 25-26 26-27 27-28 28-29 29-30
Urticaria
Cylindruria
Albuminuria.
Nitrogen Exchange in gms
Blood urea. mgm. per 100 c.c.
Urea Index
Intake
Output
200
180
160
140
120
100
80
60
40
20
0
Urine Chloride.
Phthalein
Intake
Output
%
gms
12
10
8
60 6
40 4
20 2
0 0
Water Exchange.
Weight
Intake
Output
lbs.
c.c.
133 2000
131
129
127 1000
125
123 0

CHART I

toms the chlorides disappeared entirely from the urine and were not excreted for a week. The water output diminished, the phthalein output fell from 60 to 28, the blood urea rose from 13.3 to 40 mgm. per 100 cc., the urea index fell from 90 to 1.3 and the renal function during the attack was similar to that of a severe nephritis with retention of water, salt and nitrogen. With recovery the nitrogen and salt were excreted in great excess and the renal function rapidly returned to normal (see chart 1.) A mild albuminuria and cylindruria has, however, persisted.

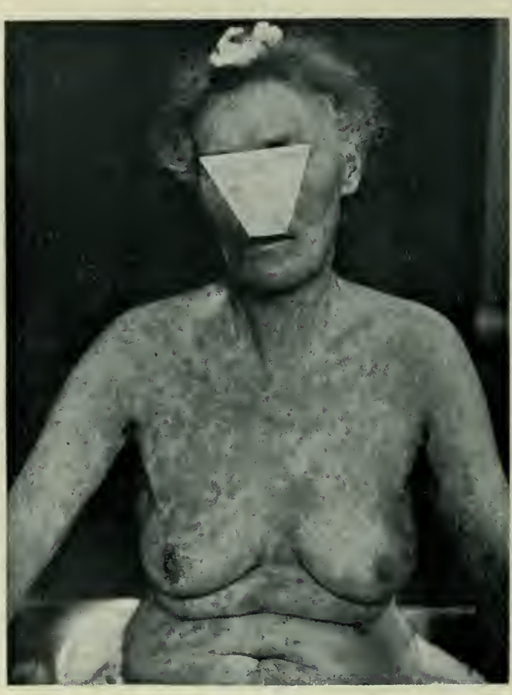

FIG. 2 CASE VI

Distribution, extent and character of eruption during acute attack of erythema multiforme

Further study showed that this patient gave a well marked skin reaction to beef serum and a moderate reaction to sheep serum but no reaction to the other proteins tested. On two occasions since September 1916 he has had a mild recurrence, one of which came on after eating a minced meat sandwich; the other attack he thinks was not associated with the eating of any form of food.

Case 6. Mrs. A. H., age 58. Admitted to the Presbyterian Hospital on October 2, 1915, with a complaint of diarrhoea and weakness of five days' duration. The diagnosis of uremia had been made before admission to the hospital. She was married, had two healthy children, had never been ill before and had never suffered from a similar illness. Five days before admission she had been suddenly seized with chills, fever, headache, and diarrhoea. There had been ten watery movements a day, but no abdominal pain. There had been no urinary symptoms until the day before admission, when she ceased to void urine. On admission the patient was prostrated and had evidently lost weight. The skin was dry and smooth. The general physical examination showed nothing further. The eye grounds were normal. The blood pressure was 130 systolic; 60 diastolic. The leucocyte count was 9400; the Wassermann reaction was negative; 100 cc. of pale amber urine was obtained by catheter, it contained much albumen and many hyaline and granular casts. Large quantities of salt solution were given by rectum and 750 cc. subcutaneously. Her general improvement was rapid until October 8, six days after admission and eleven days after onset of the diarrhoea, when she developed a profuse and generalized urticaria and erythema which persisted for six days until October 14. There were no joint pains. The lymph nodes and spleen were not enlarged. During the period of eruption the blood pressure was low, 90 systolic; 75 diastolic. The leucocytes which before had been normal, rose at this time to 44,600 with 76 per cent polymorphonuclears. With the disappearance of the eruption they fell rapidly to 8000 but at this time the eosinophiles rose from 2 per cent to form 23 per cent of the leucocytes. The chart shows the changes in concentration of blood urea, the index of urea, excretion and the output of phthalein, water and chlorides during and after the illness (chart II).

The striking characteristics are the extremely high blood urea with low index of excretion, low phthalein output and retention of chlorides and water together with the marked albuminuria and cylindruria during the illness with rapid return to normal after recovery. Unfortunately, it was not determined whether or not this patient was susceptible to any foreign protein but the clinical course of the disease with the appearance of eruption ten days after the onset of the first symptoms so closely simulates a severe serum sickness, that temporarily we have placed the patient in this group of cases.

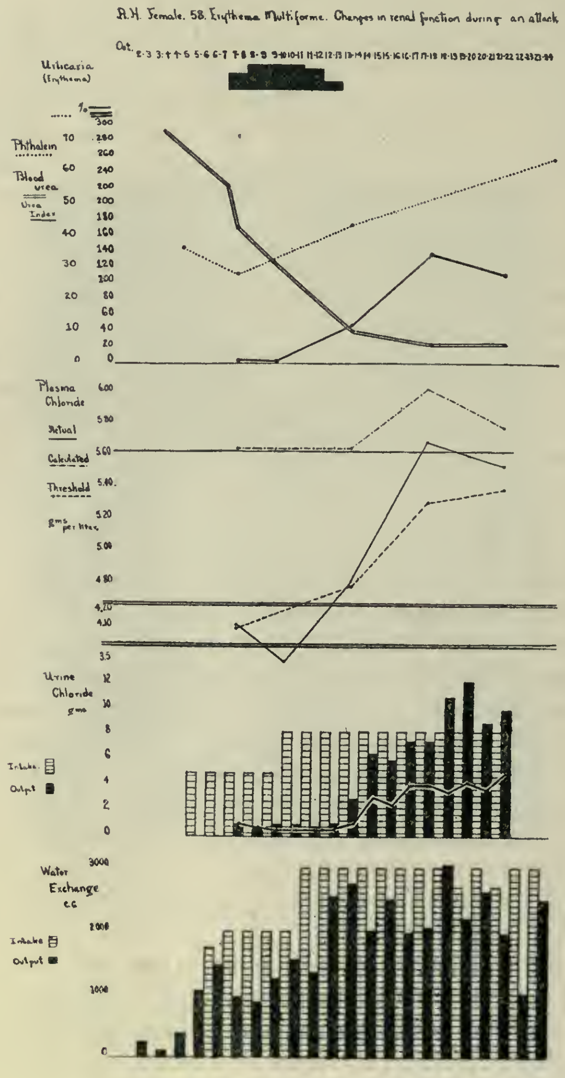
R.H. Female. 58. Erythema Multiforme. Changes in renal function during an attack
Oct. 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16 16-17 17-18 18-19 19-20 20-21 21-22 22-23 23-24
Urticaria (Erythema)
%
Phthalein
Blood urea
Urea Index
70 60 50 40 30 20 10 0
300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0
Plasma Chloride
Actual
Calculated
Threshold
gms per liter
6.00 5.80 5.60 5.40 5.20 5.00 4.80 4.70 4.10 3.5
Urine Chloride gms
Intake
Output
12 10 8 6 4 2 0
Water Exchange cc
Intake
Output
3000 2000 1000 0

CHART II

The possibility that dehydration from loss of water through diarrhoea might account for some of these alterations has been taken into account, but the persistence of these changes after the patient had received large quantities of fluid and the absence of similar changes in one case of dysentery with severe diarrhoea, makes it seem highly improbable that dehydration alone could have had much influence in producing the picture of renal insufficiency with nitrogen retention.

A summary of the examination of the urine and blood in these six cases is tabulated in table 1.

The first three cases may be dismissed without further discussion, since the attacks of urticaria, eczema and angioneurotic oedema were not associated with any disturbances in renal function or with retention of water, chlorides or nitrogen. In the fourth case the only disturbance in renal function was the constant excretion of large quantities of albumen and of casts. Furthermore it cannot be definitely shown that this condition was originally caused by the anaphylactic shock from which the patient had suffered a few months previously.

In the fifth and sixth cases there can be no doubt that the transient but pronounced nitrogen and salt retention and the simultaneous depression of the renal function were directly connected with the intoxication from which the patient suffered and formed as striking a part of the disease as the skin eruption itself.

These cases bear a close resemblance to the group which Osler (5) has so well described and which are characterized by recurring attacks of erythema, urticaria, angioneurotic oedema and purpura associated with changes in the internal viscera. The visceral lesion in a fair proportion of such cases is nephritis. Very little attention has, however, been paid previously to the protein hypersensitiveness, the functional disturbances of the kidney or to the protein metabolism in such conditions. Pepper (6) has recently reported an instance of angioneurotic oedema in a patient suffering from chronic nephritis in whom the attacks of angioneurotic oedema were accompanied by a retention of nitrogen. The retention was more marked during the attacks than in the intervening periods. The attacks were preceded by a

TABLE 1

	CASE	AGE	DATE	URINE		PHTHALEIN	BLOOD UREA, PER 100 CC.	UREA INDEX (MCLEAN)	PLASMA CHLORIDES	CHLORIDE EXCHANGE	WATER EXCHANGE	REMARKS
				Albumen	Casts							
						per cent	mgm.					
1	M. G.	30	9/14/16	0	0	63	15	126.0		Normal	Normal	Examined during attack of urticaria. Sensitive to phaseolin
2	E. D.	29	9/11/16	0	0	65	10	61.0		Normal	Normal	Skin tests give no reactions. Examined during attack of urticaria
3	W. S.	27	11/16/16	0	0	55	20	130.0		Normal	Normal	Sensitive to eggwhite and beef juice. Examined during acute attack of eczema
4	Dr. S.	32	2/ 4/15	++	++	52	17	102.0		Normal	Normal	Sensitive to phaseolin, ragweed, goldenrod, red-top, timothy, strawberry. No urticaria at time of examination
												Sensitive to beef serum
5	H. J.	45	6/26/16	+	+	18	98	5.47		Neg. bal.	Neg. bal.	During attack
			6/30/16			37	49	62.0		Pos. bal.	Pos. bal.	During recovery
			9/19/16	+	0	59	13	87.0		Normal	Normal	Before attack
			9/22/16	+	+	28	49	1.2		Neg. bal.	Neg. bal.	During attack
			9/25/16	+	0	56	20	175.0		Pos. bal.	Pos. bal.	After attack
6	A. H.	58	10/ 4/15	+++	++		295			Neg. bal.	Neg. bal.	No skin reactions made
			10/ 5/15	++	+	36				Neg. bal.	Neg. bal.	
			10/ 7/15				222			Neg. bal.	Neg. bal.	
			10/ 8/15			28	172	3.7	4.1	Neg. bal.	Neg. bal.	Erythema multiforme
			10/10/15	+	+		124	3.3		Neg. bal.	Normal	Erythema multiforme
			10/13/15	+	+	43				Neg. bal.	Normal	Erythema multiforme
			10/14/15	+	+		41	46.5	4.8		Normal	Fever. Cessation of erythema
			10/18/15	±	0		22	136.0	5.68	Normal	Normal	Well
			10/22/15	0	0		23	111.0	5.54	Pos. bal.	Pos. bal.	Well

decreased elimination of chlorides and followed by a corresponding excessive excretion.

In our group of cases it is very probable that the attacks of urticaria, eczema and erythema in cases 1, 3, 4 and 5 were caused by an intoxication similar to mild anaphylactic shock brought about by absorption of protein to which the patient was naturally hypersensitive. Case 6 is added to this group from analogy, for no examination was made to determine whether or not this patient was hypersensitive to foreign protein.

To explain the acute renal insufficiency with rapid rise in blood urea followed by prompt return to normal conditions with excessive excretion of nitrogen in cases 5 and 6, two factors must be taken into consideration; first, the general metabolic disturbance; second, the actual kidney insufficiency. For it is possible that either one or both of these factors in combination may have been responsible for the condition.

Studies by Major (7) of the nitrogen excretion of rabbits during and after anaphylactic shock, have shown that immediately after the shock there is a retention of nitrogen which gives place in twenty-four to forty-eight hours to an excretion in great excess. The work of Jobling, Petersen and Eggstein (8) has shown that anaphylactic shock in dogs is accompanied by a rapid rise in the non-coagulable nitrogen and amino acids of the blood. Cooke, Rodenbough and Whipple (9) studying the effect of proteose injections in dogs have found during the period of intoxication a rapid rise in the non-coagulable nitrogen of the blood. In a later communication Whipple and Cooke (10) have shown that shortly after proteose injections in fasting dogs, there is a well marked increase in the excretion of nitrogen which continues three to four days. Similar changes were observed in dogs after the production of a closed intestinal loop, and following intestinal obstruction both in dogs and in human beings. Whipple and his coworkers do not believe that the alterations of protein metabolism and the increase in blood nitrogen can be accounted for by a retention of nitrogen, for there was no evidence to show that the functional activity of the kidney was impaired, and therefore, conclude that these changes are dependent upon unusual destruction of body protein during the proteose intoxication.

It is highly probable that a similar disturbance in protein metabolism was produced by the intoxication in cases 5 and 6 of this series and that the increase in blood urea and the retention of water and chlorides were not wholly dependent upon an acute renal insufficiency. In support of this idea is the fact that during the period in which chlorides were absent from the urine in case 6, the concentration of chlorides in the plasma was extremely low, only 4.8 grams per liter, and consequently the retention could not be attributed at this time to impermeability of the kidney for chlorides.

Besides this general disturbance from the intoxication there was undoubtedly some transient but severe injury to the kidney which impaired its normal function. This was evident from the appearance of large amounts of albumen, and casts in the urine, the lowered excretion of phthalein and the extremely low index of urea excretion. It is obvious also from the work of Lewis (11) that this is the exact opposite of what is found during many acute infections when the excretion of phthalein and urea is above rather than below normal.

The disturbances produced by protein intoxication or anaphylactic shock in the spontaneously hypersensitive individual seem, therefore, to produce a complicated effect disturbing acutely not only the nitrogen and chloride equilibrium of the body cells but affecting the kidney, as well, and resulting in a transient renal insufficiency. The combination of these factors produces a picture closely simulating acute nephritis in some of its phases, and it is not inconceivable that attacks of this sort repeated often enough or continued long enough would result in a condition indistinguishable from nephritis. It is fairly certain that the majority of cases of acute nephritis are associated with an acute infection, either local or general, but it is also quite certain that metastatic foci of pyogenic bacteria in the kidney under ordinary conditions do not give rise either to an acute diffuse nephritis or nephrosis. It might be suggested that the mechanism is much the same as that which takes place in the individual hypersensitive to foreign proteins. The reaction in the kidney might be closely analogous to the cutaneous tuberculin reaction, and the peculiar inflammation of the kidney structures be dependent upon an altered reaction or allergy of these structures towards the soluble protein products of bacterial growth or to the protein of the bacterial bodies themselves.

Under such conditions the typical inflammatory reaction of the glomeruli or interstitial tissue of the kidney could occur only when two conditions were fulfilled, namely, the presence of an infecting agent and an altered reaction of the tissues: an allergy or hypersensitiveness to this agent.

SUMMARY

A study of the renal function in six cases of urticaria, four of which were hypersensitive to one or more foreign proteins, showed more or less profound disturbances of the functional activity of the kidney in three instances.

In one case the disturbance was limited to a marked albuminuria and cylindruria.

In two cases the attacks of urticaria and erythema were accompanied by albuminuria, cylindruria, increase in blood urea, profound depression of the index of urea excretion, decrease in the output of phenolsulphonephthalein and retention of chlorides and water.

These observations show that during severe attacks of urticaria and erythema multiforme in the spontaneously sensitive, a much more profound intoxication of the body tissues takes place than can be demonstrated in the usual case of serum disease.

It is probable that the intoxication causes a general disturbance in protein metabolism as well as an injury to the kidney.

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LYMPHOID AND CYSTIC BODIES IN THE URETHRA AS AN EVIDENCE OF TUBERCULOSIS[1]

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The early recognition of infection is frequently attended with considerable difficulty. The disease in its initial stages may cause few and slight symptoms and definite organic change be impossible of demonstration. In these cases, unfortunately, it frequently becomes necessary to withhold our judgment until further development of the malady makes the differential diagnosis possible. These difficulties in early diagnosis are frequently encountered in tuberculosis of the genito-urinary tract and there are few diseases wherein an early recognition of the condition is more important.

It is probably safe to state that renal tuberculosis is rarely demonstrated in its first two years, and often not for five or six years. The treatments applied to tuberculosis of the bladder, prostate and seminal vesicle before the true nature of the disease is discovered are usually about the worst that could be imagined, and often are calculated to induce a generalized tuberculosis. This, I think, will be admitted by most urologists and is ample argument for the closest study of the lesions I am about to describe. My own belief, based upon studies during the last three and one-half years, is that, when present, they are invariably local manifestations of a more or less active tuberculosis elsewhere in the body, and yet time and future studies may show that there are conditions other than tuberculosis that can cause them.

If the cystoscope, with the lens on the convex surface, is inserted into the bladder, and, with the irrigating fluid flowing, the fenestration is drawn into the posterior urethra, it will be found that a very good view can be obtained, almost as good as that given by the cysto-urethroscope. By rotating the instrument so as to bring the lateral urethral wall into view, there will occasionally be seen a number of small, slightly pedunculated, or sessile, masses of tissue springing from a mucosa that seems little, if at all, inflamed. These bodies vary considerably in size, are of a pearly white, rarely red, color, and minute blood vessels can be seen traversing their smooth unbroken surfaces. At an early stage, these are apparently solid masses of tissue that later seem to undergo a cystic change. In this cystic stage they are easily ruptured, and a whitish substance exudes. When ruptured, they leave an abraded reddish surface, usually circular in outline, with a small shred of white tissue attached to the edge. Such areas may be the only evidences of

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[1] Read, by invitation, before the annual meeting of the American Urological Association in Chicago, April 2, 1917.

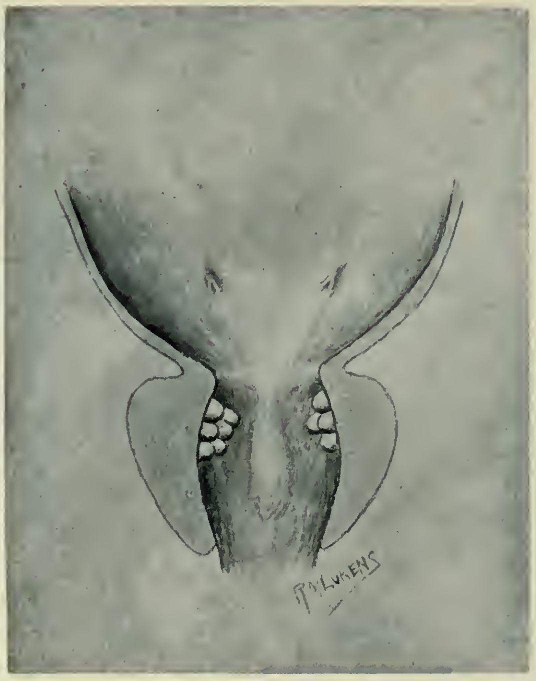

Fig. 1. The Usual Location of the Urethral Bodies (Diagrammatic)

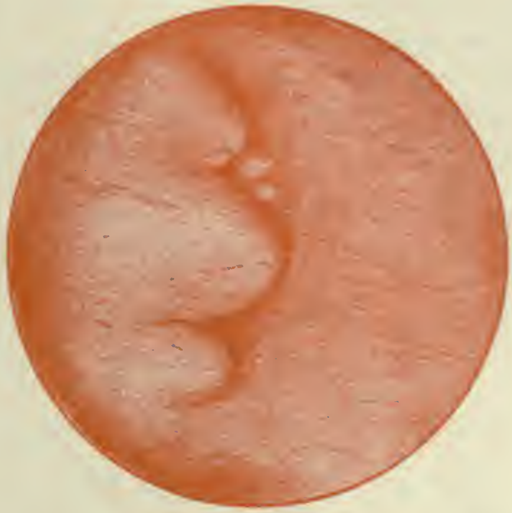

FIG. 2. CYSTOSCOPIC APPEARANCE OF THE LESIONS

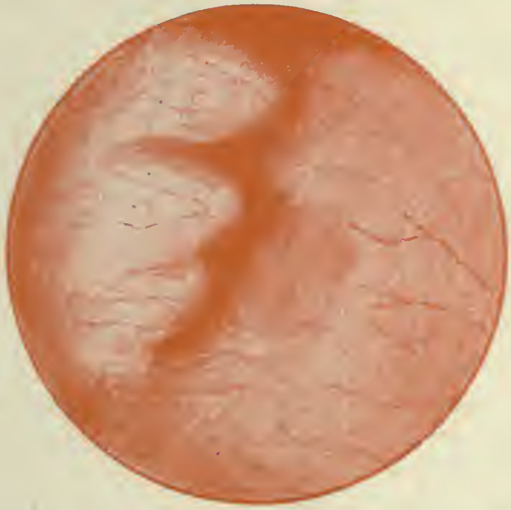

FIG. 3. CYSTOSCOPIC APPEARANCE OF THE LESIONS

urethral trouble and should excite suspicion. A future study will, in all probability, reveal the solid masses and the true nature of the condition.

While the location of these bodies is usually upon the lateral urethral walls, just distal to the vesical neck, they may occur upon almost any portion of the prostatic urethral wall or verumontanum. I have observed them, upon one occasion, just distal to the bulbo-membranous junction of the urethra. They also occur in the anterior trigonal angle and urethra of the female.

The magnification of the cystoscope for near objects, and the pressure of the irrigating fluid and instrument, however, mislead as to the true size of the lesions and the color of the mucosa, for, when studied at autopsy, the lesions are found to be minute excrescences, measuring from 1 to 3 mm. in diameter. They are pink or yellowish in color, and surrounded by a distinct red areola.

Histologically, as will be seen by the photomicrographs, they are typically tuberculous tissue, and show the inherent tendency of such tissues to caseate. In the zones surrounding the areas of caseation, tubercle bacilli may readily be demonstrated.

A persistent search upon my part for a postmortem specimen was unsuccessful. It has, however, been the good fortune of Dr. Alexander Randall, with his greater opportunities in this field, to find four such specimens. He has very kindly furnished me with a full description of the first specimens, from which I am pleased to quote as follows:

Male, white, 26 years of age. Clinical diagnosis, pulmonary tuberculosis. Pathological diagnosis, chronic pulmonary tuberculosis (conglomerate and ulcerative); tuberculous pleurisy, enteritis, cystitis, urethritis and nephritis (left), with the usual evidences of prolonged toxemia in other structures. Bladder and urethra. At the left ureteral orifice are found two or three small ulcerations, practically confluent, measuring 7 by 4 mm., and about 1 mm. in depth. The edges are slightly undermined, irregular and partially necrotic. The ulcer base is fairly clean, dark red in color, with slight slough; there is a moderate amount of injection of the mucous membrane about this

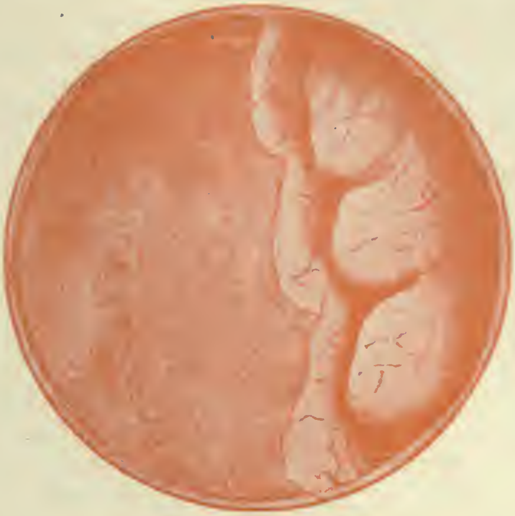

FIG. 4. CYSTOSCOPIC APPEARANCE OF THE LESIONS, SHOWING PROXIMITY TO THE VESICAL SPHINCTER

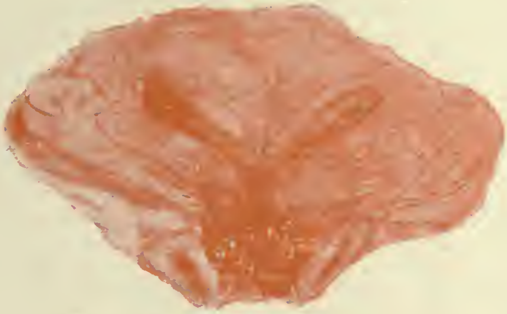

FIG. 5. DRAWING MADE FROM ONE OF DR. RANDALL'S SPECIMENS

The injection of the urethral mucosa around the masses is distinctly seen. It is continued over the trigone, blending with a red area surrounding the right ureteral orifice.

ulceration. Higher on the left wall of the bladder are found three small ulcers, the largest approximately 5 by 3 mm., while on the anterior wall, to the right of the midline, are four small isolated ulcerations. The trigone supports one ulceration 1 cm. below the left ureteral orifice and of small dimensions, while on the uvula vesicae a pin-head sized ulcer is found. There is no diffuse tuberculous cystitis. The posterior urethra presents a solitary ulcer on its left wall, measuring 5 by 4 mm. in extent, and similar in character to those in the bladder wall. Thickly spread over the posterior urethra, especially over the urethral trigone and right lateral wall, appear many small papillary growths or excrescences, usually about 1 to 2 mm. in diameter. These excrescences are a pale creamy white in color, and stand out sharply against the injected mucous membrane. They are found more or less thickly over the entire posterior urethra and verumontanum, but absent in the neighborhood of the above-mentioned urethral ulcer. The prostate and seminal vesicles are grossly devoid of tuberculous involvement.

A section of tissue taken from the prostatic area of this specimen gives no hint of involvement beneath the mucosa. The accompanying photo-micrographs, made from these sections, show very clearly the character of the lesions.

In a previous article (The New York Medical Journal, October 16, 1915) entitled "New Growths of the Prostatic Urethra in Relation to Tuberculosis," I reported the histories and clinical and laboratory findings of nine cases. For the purpose of making the present report as complete as possible, I shall include these cases. For the sake of brevity they will be tabulated, as the previous histories are more or less similar.

That the condition is by no means a rare one is evidenced by the fact that in approximately 3500 cystoscopies within the last three and one-half years, I have seen 51 cases. Of this number, I have had the opportunity to study 42 cases, of which 37 show reasonably certain evidences of tuberculosis. Five are still being studied for further confirmation of a coexisting tuberculous focus. Nine of these cases were observed only once, and did not return for further study.

The most striking points in the entire group of cases are the following.

1. Many were, or had been, in direct daily contact with cases of tuberculosis.

2. Thirty-two had had a more or less recent specific urethritis.

3. Almost all of this latter number were being treated for "chronic urethritis."

4. The urine was usually clear but contained shreds.

5. An associated follicular prostatitis was the rule.

6. Frequency of urination was present in 21 cases.

7. Burning pain in the fossa navicularis was present in 35 cases, usually only at urination. It was the most common symptom calling attention to the lesions.

8. Burning pain at the vesical neck or in the perineum, either constant or intermittent, was present in 19 cases.

From the standpoint of symptomatology, these patients can be very readily divided into four distinct groups:

Group I. Those cases with a previous history of gonorrhea, entirely free from subjective symptoms, but with a morning drop and few shreds in the urine. These cases are discovered only through routine cysto-urethroscopic studies. Physical appearance rarely suggests tuberculosis.

Group II. Those cases, with or without a previous gonorrhea, in which there is a slight burning in the fossa navicularis upon urination, a morning drop and a shreddy urine. The burning suggests the advisability of study, and physical appearance only occasionally suggests tuberculosis.

Group III. Those presenting burning at the vesical neck and occasionally in the fossa navicularis, frequency of urination, an anterior discharge and a shreddy urine. Physical appearance quite often suggests the nature of the malady.

Group IV. Those presenting any or all of the foregoing symptoms and a turbid urine. The first impression of these cases is that of a well-advanced tuberculosis. They are in the minority.

As to the entire significance of these lesions, I fear that it is too early to make a positive and final statement. Whether or not future studies will prove that they appear only in certain cases with renal tuberculosis is a question of much interest from both a diagnostic and prognostic standpoint. If time proves such to be the case, their finding will be a matter of the greatest importance to such patients, and that this may be the case is, in a measure, hinted by the results of my studies. Three of the patients under observation have developed unmistakable signs of renal tuberculosis that could not be found when they were first seen. The urethral lesions are, as a rule, what might be

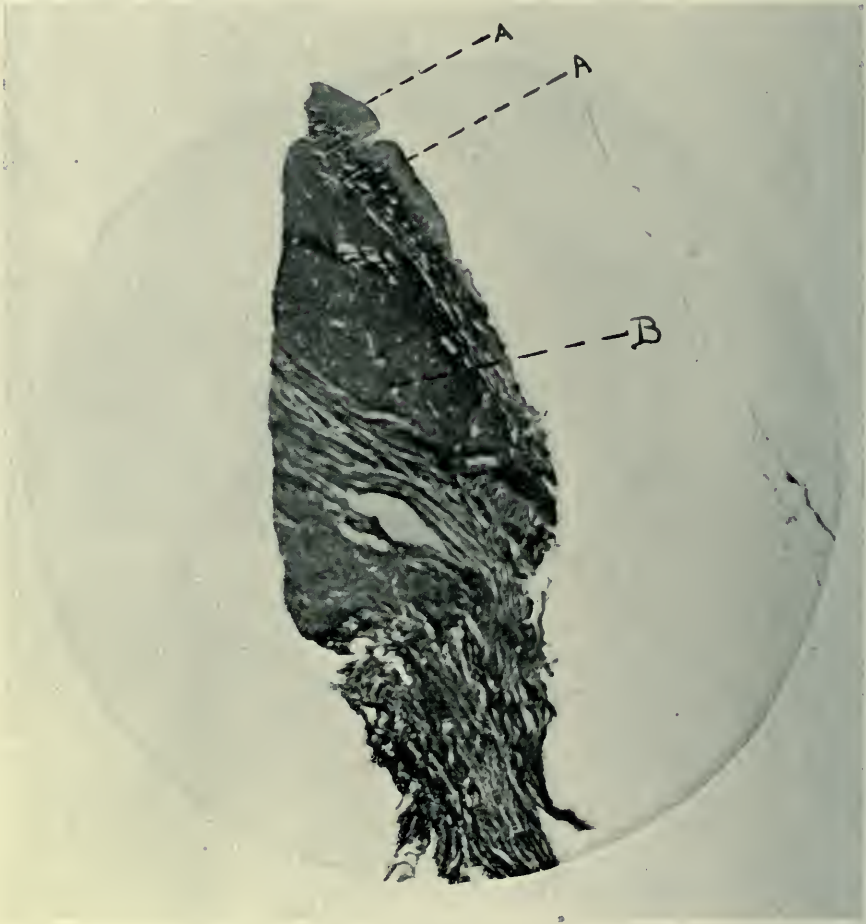

Fig. 6

A, Urethral mucosa presenting two of the excrescences, *B*, portion of the anterior prostatic commissure.

called "closed lesions," as ulcerated surfaces can rarely be seen. They probably are not a common factor in the appearance of tubercle bacilli in the urine, which is not an uncommon finding.

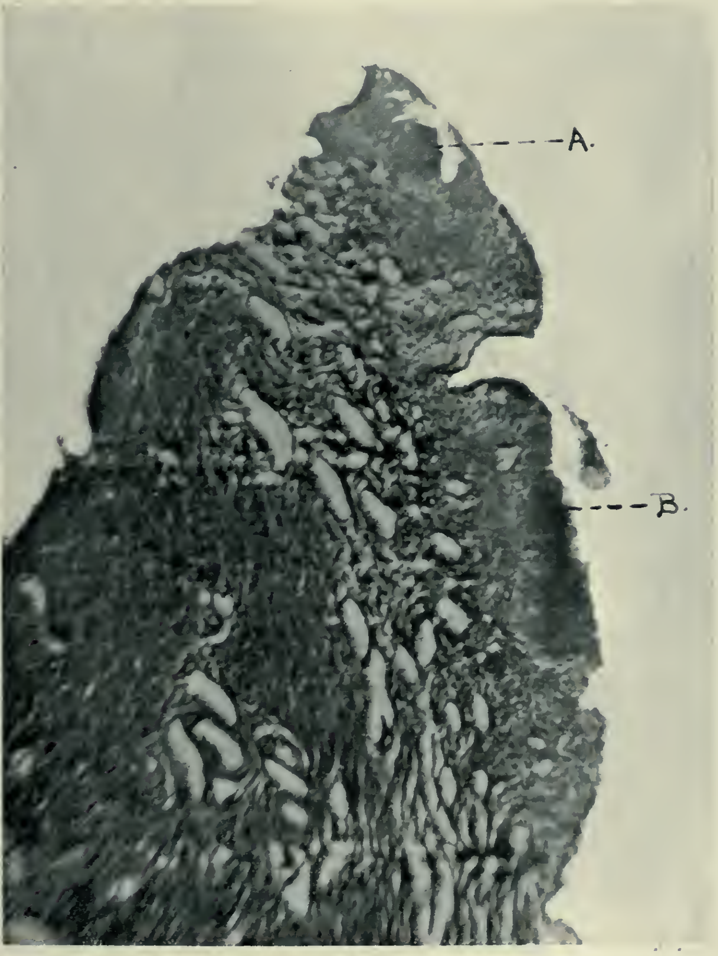

Fig. 7. Higher Magnification of Figure 6, Showing Necrotic Areas at *A* and *B*

There is little reason to believe that the underlying prostate is tuberculous, as the urethral mucosa alone seems involved, and, as I have been unable to find the bacilli in any of the expressed prostatic secretions examined, the natural assumption is that the gland is not a frequent source of the organisms. The same might be said of the seminal vesicles, as in only two of the cases presenting tubercle bacilli in the urine was there any evidence of disease of these structures obtainable. I am thus led to the con-

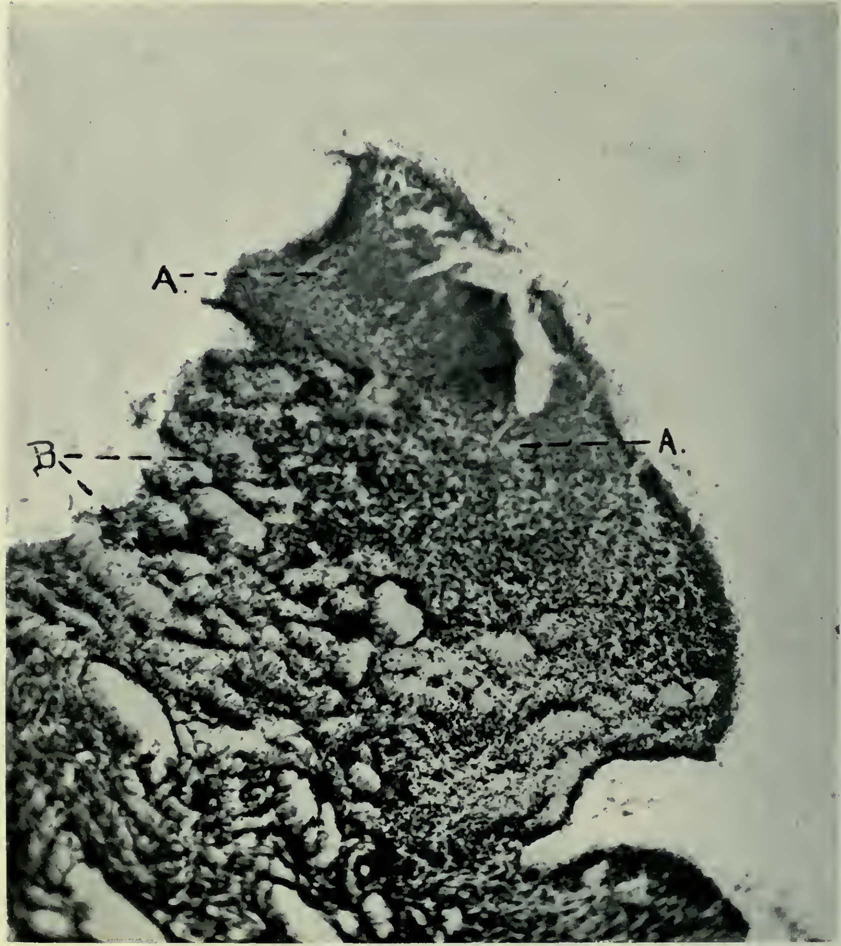

Fig. 8. Still Higher Magnification of Upper Portion of Figure 7
A, Zones in which tubercle bacilli were demonstrated; *B*, normal prostatic tissue.

clusion that these bacilli come either from or through the kidney; that they can pass through a non-tuberculous kidney seems

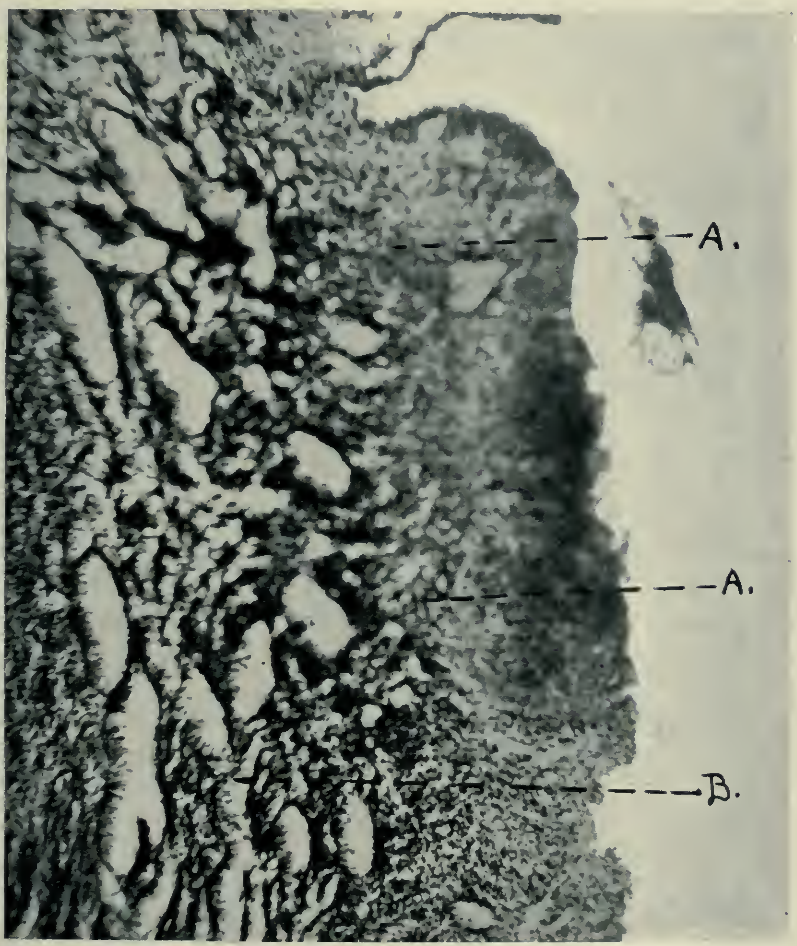

FIG. 9. HIGHER MAGNIFICATION OF LOWER PORTION OF FIGURE 7
A, Zones containing tubercle bacilli; *B*, normal prostatic tissue.

to be fairly well shown, but that they often do, is, I think, doubted by most urologists.

Although there may be tubercle bacilli in the whole urine when these lesions are discovered, it is often impossible to say that this or that kidney is the seat of disease, as the catheter specimens give no evidence of change, except, perhaps, an excessive number of small epithelial cells, the urea and phthalein outputs being evenly balanced. A slightly reddened ureteral meatus upon one side is often encountered, which, though significant, is only sufficient to cast suspicion upon that kidney, for if it is an evidence of disease, it appears before such a lesion can be demonstrated by diagnostic means now at our disposal.

As will be seen by a study of the tabulated cases, the most frequent demonstrable accompanying lesion has been in the lungs, the kidney, the bladder and the epididymis, in the order named.

From these studies, a number of more or less definite statements may be made by way of a summary:

1. There are many cases of advanced urogenital and pulmonary tuberculosis in which these lesions are not present. They have, therefore, no negative value.

2. They are not peculiar to the male, as case XXV was a woman who presented the lesions in the anterior trigonal angle and urethra, and had many tubercle bacilli in the urine from each kidney. Several years ago, I recall having removed by fulguration similar growths from the urethra of a woman, under the impression that they were papillomata. This woman now has a moderately advanced tuberculosis.

3. At least 80 per cent of these patients were in apparently robust health and had never been suspected of any form of tuberculosis.

4. I am of the opinion that these bodies appear very early, and they apparently persist throughout the entire course of the tuberculosis. They have been found in the mildest, as well as the most advanced, phases of the disease. With two possible exceptions, they have not disappeared in any of the cases I have been able to follow, and where the cystic forms have been entirely broken up by instrumentation, they have recurred in less than two months.

5. From their absence one and one-half years after a nephrectomy in case IX, it is evident that they bear the same relation

to such an operation as does vesical tuberculosis, and are in no sense a contra-indication to it.

6. There is evidence (cases V and VII) to support the belief that persistent prostatic massage, though indicated by the coexistent prostatitis, has a decided tendency to light up tuberculous foci in other parts of the body, particularly in the lungs and epididymi.

7. Probably 50 per cent (or more) of all cases of chronic follicular prostatitis, which present as a symptom burning at the vesical neck or in the fossa navicularis, on voiding will show these urethral bodies, and have tuberculosis. This would suggest more than coincidence as to the rôle of gonorrhea in encouraging tuberculous invasion. Following this thought, it is safe to say that any case presenting either of these symptoms, not directly due to some treatment or acute inflammation, requires a cysto-urethroscopic study, and to withhold it is to do the patient a gross injustice.

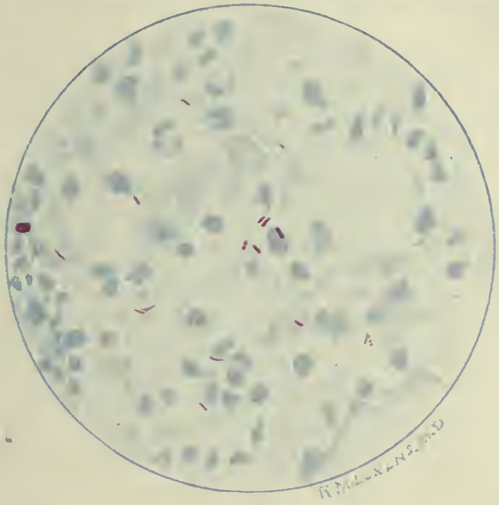

Fig. 10. Drawing from *A*, Figure 8, Showing Tubercle Bacilli in the Tissue

8. Sufficient time has not elapsed to venture an opinion as to prognosis, but it has been abundantly impressed upon me that

most of these patients do very well if local treatments to the urethra and prostate are avoided, and anti-tuberculous treatment is instituted.

9. Thirty-seven out of forty-two cases studied showed strong evidence of tuberculosis, and three of the autopsy specimens found by Dr. Randall were from patients dead of the same disease; sections of tissue removed from the urethrae of two of the living patients show tuberculosis with demonstrable bacilli. Therefore, it is felt that there is ample evidence to support the contention that these bodies are truly a manifestation of tuberculosis.

In these studies, I have been particularly fortunate in having the kind help of Dr. Randle C. Rosenberger with the laboratory studies, Drs. E. J. G. Beardsley and G. H. Clapp have assisted me in the medical aspects of the cases, and it is a pleasure to acknowledge my indebtedness to them. I desire, also, to express my thanks to Dr. Alexander Randall for his very kind and able description of the postmortem specimen in his possession, to Dr. Wm. M. L. Coplin for the photo-micrographs, to Drs. R. M. Lukens and F. F. Hanbidge for drawings, to Drs. H. R. Loux and J. Chalmers DaCosta for the privilege of reporting cases from their respective services, as well as Drs. T. C. Stellwagen, Jr., Chas. W. Bonney and W. H. Kinney for permission to study and report private cases of theirs.

CASE NUMBER	INCREASED FREQUENCY	BURNING PAIN AT VESICAL NECK OR IN PERINEUM	BURNING PAIN IN FOSSA NAVICULARIS	TUBERCLE BACILLI IN THE URINE	PROBABLE TUBERCULOSIS ELSEWHERE	REMARKS
I	Yes	Yes	Yes	Yes	?	
II	Yes	Yes	Yes	Yes	?	
III	Yes	Yes	Yes	Yes	Yes	Advanced tuberculosis upper lobe, both lungs
IV	Yes	Yes	Yes	No	Yes	Tuberculosis upper lobe, both lungs
V	No	Yes	Yes	?	Yes	Tuberculosis of lung. Tubercle bacilli in urethral tissue
VI	Yes	Yes	Yes	No	Yes	Tuberculous right kidney removed. Tuberculous left perinephritic abscess, persisting sinus; bilateral pulmonary
VII	No	No	No	Yes	Yes	Active pulmonary tuberculosis, renal and epididymis
VIII	No	No	Yes	Yes	Yes	Pulmonary tuberculosis
IX	Yes	No	Yes	Yes	Yes	Tuberculous right kidney removed
X	No	Yes	Yes	Yes	Yes	Tissue removed is typically tuberculous and contains bacilli. Extensive pulmonary lesion, apparently latent
XI	No	No	No	Yes	Yes	Chronic pulmonary tuberculosis
XII	Yes	No	No	?	Yes	Clinical evidences of tuberculosis of upper lobe, right lung. Marked loss of weight
XIII	Yes	No	Yes	Yes	?	Probable left renal tuberculosis with marked pyuria
XIV	No	No	No	Yes	Yes	Active pulmonary tuberculosis
XV	No	No	Yes	Yes	Yes	Active tuberculosis of upper lobe, right lung .
XVI	Yes	Yes	Yes	Yes	Yes	Active pulmonary tuberculosis
XVII	Yes	No	Yes	Yes	Yes	Pulmonary tuberculosis, now apparently latent
XVIII	No	Yes	Yes	?	Yes	Tuberculosis of upper lobe, left lung
XIX	Yes	Yes	Yes	?	Yes	Chronic pulmonary tuberculosis. Bilateral pyuria
XX	No	No	No	Yes	Yes	Tuberculosis of both lungs. active. Tuberculous granulomata of bladder

CASE NUMBER	INCREASED FREQUENCY	BURNING PAIN AT VESICAL NECK OR IN PERINEUM	BURNING PAIN IN FOSSA NAVICULARIS	TUBERCLE BACILLI IN THE URINE	PROBABLE TUBERCULOSIS ELSEWHERE	REMARKS
XXI	Yes	No	Yes	Yes	Yes	Hunchback. Tuberculosis of bladder, prostate, epididymis and probable kidney. Marked pyuria
XXII	Yes	Yes	Yes	?	Yes	Extensive lesion of upper lobe, left, active. Bilateral pyuria
XXIII	No	No	No	?	Yes	Extensive chronic pulmonary tuberculosis
XXIV	No	No	Yes	?	Yes	Tuberculosis of upper lobe of right lung
XXV	Yes	Yes		Yes	Yes	Woman. Tubercle bacilli and pus from both kidneys
XXVI	Yes	Yes	Yes	?	Yes	Tuberculosis of upper lobe of right lung
XXVII	Yes	Yes	Yes	Yes	Yes	Typical tuberculous cystitis, probable renal
XXVIII	No	Yes	Yes	?	Yes	Tuberculosis of upper lobe of lung, active ;
XXIX	Yes	Yes	Yes	Yes	Yes	Old lesions in both lungs. Evidences of right renal tuberculosis with bladder involvement
XXX	Yes	Yes	Yes	Yes	Yes	Typical tuberculosis of bladder with undoubted left renal involvement
XXXI	No	Yes	No	?	Yes	Pulmonary tuberculosis, active
XXXII	No	Yes	No	?	Yes	Chronic pulmonary lesion
XXXIII	Yes	No	Yes	?	Yes	Lesion of upper lobe of right lung, probably latent
XXXIV	No	No	Yes	?	Yes	Pulmonary tuberculosis in upper lobe of both lungs, active
XXXV	Yes	Yes	Yes	?	Yes	Extensive chronic pulmonary tuberculosis. Renal, bladder and prostatic tuberculosis. Marked pyuria
XXXVI	Yes	Yes	No	?	Yes	Great loss of weight, prostration, night-sweats for two months. Renal hematuria
XXXVII	No	No	No	?	Yes	Probable pulmonary tuberculosis, also pleurisy

MEDIAN BARS AS FOUND AT AUTOPSY[1]

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I fear there is very little uniformity of opinion as to what constitutes, and what we individually mean, when we speak of median bar formation. There are already some nine different titles used by various authors to designate apparently the same condition, and a review of the literature leaves one's mind in a rather confused state of misinformation.

However on close scrutiny one finds that the symptomology is well understood, the diagnosis easy and well defined, and the treatment definite and its results good, so that we are left with but the gross and microscopic pathology, and the terminology, as bones of contention and misunderstanding. What does the man mean who writes of "Sclerosis of the internal sphincter?" Is he writing of the same condition as the one whose title is "Contracture of the vesical neck," or he whose title is "Atrophy of the prostate," or perhaps "Atony of the senile bladder?" I personally believe that they are all speaking of one and the same condition, as they individually met it in their patients, that is clinically, and the one criticism that I would make of the majority of these contributions (and titles), is that they are based on clinical experience alone, unbacked by pathologic study of the diseased tissues, and yet have had applied to it titles that signify the pathologic changes that are present, or are supposed to be present.

Clinical terminology is very valuable and especially descriptive, but a very fickle mistress if not wedded to pathology, and its use here has led to the confusion of ideas as to the pathology of median bar formation. The confusion would have been avoided if others had only followed the lead of the original observer and had applied but a pure clinical phrase or title "Bar formation," until they had some definite microscopic work on which to base their assumption that it was a certain pathologic change.

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[1] Read at the meeting of the American Urological Association, Chicago, 1917.

I thought when I undertook this work, which consists of the gross study of prostates and bladders as they came to autopsy, irrespective of age or clinical diagnosis, that I had a very good and clear idea of what a median bar was, its appearance, its topography, its consistency, et cetera, and I was fortunate in that the first ones encountered were of the classical or typical variety. This type was the pure sclerotic or fibrous variety of median bar, and the one which is probably meant when most of us speak of median bar formation. But as time went on and more specimens were encountered, I found that I had to modify, and still further modify, my conception of what a median bar was, until, as I address you today, I use the term in a very broad sense, meaning thereby, obstructions involving the posterior vesical lip, unassociated with changes of an obstructive character elsewhere in the prostate, bladder, or posterior urethra. Very early in the work I was confronted by a second type of obstructive change that was definitely glandular in character and an hypertrophy. This immediately divided the bars into two varieties, the fibrous on the extreme one hand, and the glandular on the extreme other hand. As the material accumulated, borderline cases arose, midway between these two extremes, where often with the specimen in your hand, you could not tell whether you were dealing with the fibrous variety or the glandular. These cases demanded microscopic study and such was undertaken. The latter has proven to a certain extent the correctness of the deductions drawn from the gross macroscopic study alone, and has likewise shown that there are borderline cases where sclerosis and glandular hypertrophy are mixed, and hence we cannot be too exacting in nomenclature and classification. For this reason I have held to a classification based on the gross pathologic changes, rather than on the microscopic, as from a clinical viewpoint it is the best working basis. Moreover I have also adhered to the title "Median Bar Formation" because the work has shown that the pathology varies, and personally I am strongly in favor of retaining this title, limiting it by an adjective to designate the type of pathologic change that has caused the bar in any specific instance. Likewise I will describe, in the following pages, the four main types of obstructive changes that have been encountered, speaking of each as though it occurred as a pure pathologic picture, but asking you to remember that though the gross picture is frequently typical of its type, the microscopic pathology is often mixed.

There have now been examined a total of three hundred autopsy specimens, with ages varying from eighteen to eighty-three years. Studying them by decades we find that

	cases
From 10 to 20 years there were	4
From 21 to 30 years there were	33
From 31 to 40 years there were	59
From 41 to 50 years there were	76
From 51 to 60 years there were	57
From 61 to 70 years there were	48
From 71 to 80 years there were	15
From 81 to 90 years there were	2
And of age unknown there were	6
Total	300

These three hundred autopsy examinations have uncovered fifty-four cases of obstruction at the posterior vesical lip, that is specimens of median bar formation, under the definition given above. Eighteen per cent of the total number of specimens examined showed obstruction of this type.

Of the fifty-four median bar cases, eighteen are recorded as large, by which I mean that there is no doubt that the condition as found must have caused urinary obstruction and retention, and that the size of the bar and the visible damage to the urinary tract above stood out as a marked abnormality on examination of the specimen. They represent 6 per cent of the total series and occurred at ages varying from thirty-six to seventy-nine years.

In the remaining thirty-six cases (12 per cent), the bar is recorded as small, meaning thereby that though the abnormality was unmistakable on examination, the condition was not of so pronounced a degree, nor was it associated with other changes that would make me feel positive that urinary obstruction of importance had yet occurred. They are simply the early cases, where development had not reached such a degree as in the previous group. In these the ages are recorded as from twenty-six to seventy-four years.

The average age for the cases classified as large bars is 58.4 years, and for the small bars 46.3 years, a difference in figures that was to be expected, but not to be considered weighty, except from the clinical and diagnostic standpoint, for with but few omissions they are all within the age when hypertrophy of the prostate may be expected to be the cause of the condition.

Realizing that a criticism of this way of approaching such a problem would be that it is devoid of any specific clinical information in these cases as to whether or not there really was any urinary obstruction present before death, I have taken particular pains in each and every case to find evidence of any back pressure in the bladder, the ureters, or the kidneys. In the majority of cases this has been so self-evident as to demand explanation rather than inquiry. The presence of beginning muscular hypertrophy and trabeculation of the bladder wall, the presence of a *bas fond*, diverticular formation, or the thin-walled, dilated bladder, are all indicative of retention and back pressure; likewise ureteral dilatation, varying grades of hydronephrosis, and changes in the renal parenchyma, have been the ear-marks that have helped to label these gross pathologic changes as having been obstructive during life. As an actual matter of fact, these and only these are ofttimes the stigmata which we use clinically to diagnose bar cases, and we really only lack as missing factors from our symptom complex the demonstration of the presence of residual urine, and the rather unreliable symptom of urinary frequency or difficulty.

Each of the two varieties of bars—the fibrous and the glandular—have had to be divided into two subdivisions, or subvarieties, making four types in all; viz.:

1. A type of bar or dam, rising from, or better stretched across, the posterior lip of the vesicle orifice, formed of firm, dense, sclerotic tissue, whose edge is sharp and narrow, and whose lateral terminations form an abrupt angle with the lateral walls of the vesical outlet. It occurs as an abrupt rise to the normal level course of the posterior urethra, and one finds that the distance from the vesical orifice to the verumontanum—the so-called urethral trigone—has been markedly foreshortened and in typical cases the verumontanum is drawn up directly under the abrupt rise that forms the median bar. On cross section the distance from the vesical lip to the perivesical tissue posteriorly is considerably increased, as is also that from the same surface to the mass of tissue that forms the posterior prostatic commissure. This latter distance is formed of a striated fibrous tissue of dull white color, devoid of apparent gland elements, and with fibres running parallel to its surfaces to meet at the bar's free edge. It gives one the impression of being pinched up, or drawn together, rather than that of proliferative outgrowth.

Microscopic. The study of sections of this type of fibrous bar have shown different degrees of an inflammatory sclerosis. In the early cases the inflammatory reaction is limited to islets of round cell infiltration under the mucous membrane and at scattered foci, ofttimes perivascular, deeper in the muscular tissue. This early stage is followed by a gradual connective tissue proliferation crowding between the muscle bundles advancing as the muscular tissue decreases, and associated with more or less generalized round cell proliferation throughout all layers and depths. Several sections have been cut of fibrous bars which apparently showed no inflammatory reaction, no roundcell infiltration, et cetera, but just a marked connected tissue proliferation and muscular atrophy: it represents I believe an end process with the inflammatory element quiescent—a fibrosis—such as is seen elsewhere in the body after a chronic infection has run its course. In none of my sections has the inflammatory process been limited to the vesical lip region alone,—I mean the sphincter muscle structure alone,—but in the depths can also be found similar changes going on in, and around, the gland acini. At times it is a progressive sclerosis with pressure atrophy of the acini and again in other sections it seems to be associated with a certain degree of hypertrophic glandular changes.

It is my firm conviction from these observations that the fibrous types of median bars are but the outward visible sign of an underlying infectious process, a chronic prostatitis, and is not the result of a limited local lesion.

Frequency. There have been four specimens of this type classified as large bars. They occurred at the ages of 58, 60, 65, and 67 years. All four had advanced chronic interstitial nephritis. The youngest died in uremia. Two had markedly trabeculated bladders, associated with diverticula formation, and the fourth had bilateral hydronephrosis and dilated ureters. There were twenty-one cases classified as small bars of this type, varying in age from twenty-six to seventy-four years.[2]

2. Is a type of fibrous bar whose projection has a tendency upward, or vesicalward, and seems to encroach upon, or draw upon, the vesical trigone more than upon the urethral surface. It causes a shortening of the vesical trigone by a transverse creasing or infolding of the same, and it is on this account the type more readily appreciated cystoscopically by the deep depression where the flat trigone should be, and by the proximity of the ureteral orifices to the vesical orifice. This type has been least frequently found in this series, and likewise shows less tendency to obstructive changes. This subvariety of fibrous bar is not essentially different from the first as to its microscopic structure, it simply seems to have expended its efforts in a different direction, and is not associated with the urethral shortening so characteristic of Type 1, but by the aforementioned trigonal change.

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[2] The large number of specimens here classified as small fibrous bars is hardly a fair proportion to draw deductions from, for some are there because early in the work I had no classification and close descriptions of the specimens are absent, and secondly I feel sure that were each and every one sectioned and studied microscopically they would be found (as some have been), to belong in other types. Judging them grossly I have no alternative than to place them here and draw attention to the fact.—A. R.

There have been five specimens of bar of this type; three classified as large occurring at the ages of 55, 65, and 79 years. All associated with chronic kidney and bladder changes, and the youngest with a dilated right ureter. The two classified as small occurred at the ages of forty-three and forty-four years.

3. This is a type of glandular bar where the hypertrophic process is confined to the gland acini of the posterior prostatic commissure, inside the prostatic capsule and under the sphincter muscle. It raises the posterior vesical lip into a thick, broad, heavy obstructing bar. I believe that this is often the most prominent feature of a beginning general hypertrophy of the prostate, and is also the early cause of obstruction to the emptying of the bladder. However it is frequently unassociated with visible hypertrophic changes—grossly—in the lateral lobes, or even if so associated it undoubtedly gives rise to obstructive manifestations long before a correlative amount of hypertrophy in the lateral lobes assumes any importance at all.

On section in the midline of one of these bars there is found a covering layer of from 6 to 8 mm. in thickness of uniform fibrous and muscular tissue. This is more than occurs in a perfectly normal vesical lip, but not comparable with the true fibrous bars. Below this is seen distinctly a circumscribed area of glandular tissue, in some cases 2 cm. in diameter. This appears whiter with the typical translucent mottling and spheroid appearance of hypertrophic prostatic tissue.

Apparently it is this type of obstruction which has been frequently spoken of as "sphincter muscle hypertrophy" as if the increase in muscle tissue was the obstructing feature. True it is that in such cases the "punch" operation and others will remove only muscle tissue, and will demonstrate that this muscle tissue is hypertrophied and increased above the normal, but when one studies these cases from post mortem specimens it is easy to show that the actual obstructive factor is the glandular hypertrophy in the prostatic commissure, and that the increase in musculature is only an effort on the part of nature to overcome the effect of the deep-seated, hypertrophic, glandular tissue. Moreover let it be realized that it is the longitudinal detrusor muscle (Bell's Muscle) that is hypertrophied and not the sphincter. (See illustrations nos. 7, 8, and 9.)

Microscopic. This type of bar has been very easy to demonstrate microscopically and in all specimens the typical picture of prostatic hypertrophy was found, limited to the posterior prostatic commissure, and within the prostatic capsule. There was likewise found a simultaneous association of inflammatory sclerosis with the hypertrophy in all the cases studied microscopically of this type of bar formation.

Frequency. There were ten cases in all put in this classification. This is 3.3 per cent of the total series of autopsies. There were four cases classified as large bars, occurring at the ages of 46, 50, 50, and 56 years. In two it must be granted that there was a slight degree of lateral lobe hypertrophy, but in no wise correlative to the size of the large glandular bar and certainly playing no part in the bladder obstruction. There were six cases classified as small bars of this type occurring at the ages of 26, 40, 50, 53, 55, and 63 years.

4. The type of glandular obstruction—call it bar if you will—caused by the isolated hypertrophy of Albarran's subcervical glands. These hypertrophies have proven to be quite frequent and rarely develop as a definite bar but rapidly assume the shape of a perfectly rounded lobe with deep lateral cleftings. Several beautiful specimens of such isolated hypertrophies have been encountered in the series varying from a small lobular mass or nodule lying in the internal sphincter's grasp, up to that of a large intra-vesical lobe, and it has been a matter of difficulty to decide whether to group them with the bar cases, where clinically they belong (when small), or under prostatic hypertrophy which anatomically they are. The small hypertrophies (ofttimes the most obstructive) can be dealt with surgically as though they were bars, while the large lobes demand procedures similar to prostatectomy, and it is to be left to each man's opinion in each individual case where the dividing line is to be drawn.

On section one sees just immediately under the mucous membrane glandular tissue of varying size according to the gross enlargement present.

Microscopic. On section of such a lobule, one sees under the microscope a proliferation of gland acini a little atypical from benign prostatic hypertrophy, in that there seems to be more of a glandular hyperplasia—an actual increase in the number of gland tubules—than a glandular hypertrophy with the typical finger-like intra-acinous projections that is found in the hypertrophic lateral lobes. This hypertrophy lies directly under the mucous membrane, and in my sections is again associated with certain degrees of inflammatory manifestations.

Frequency. The enlarged subcervical lobe has been without doubt the most frequent obstructive growth found in this series of autopsies. However I have included here only those that were absolutely devoid of any hypertrophic changes in the lateral lobes and also only those where the growth could be considered of size compatible with operative procedures now in vogue for the cure of median bar formation. Fourteen specimens have fallen into this group. Seven, or 2.3 per cent are recorded as large and definitely obstructive. They occurred at the ages of 36, 48, 56, 67, 71 and 73 years. The ones classified as small are recorded as of 43, 47, 51, 54, 56, 62 and 64 years of age.

CONCLUSIONS

1. There have been examined three hundred autopsy specimens in the adult male. They have shown median obstruction to the vesical outlet in 18 per cent, or fifty-four cases. These have been shown to be either (1) fibrous, 10 per cent, or (3) glandular, 8 per cent.

2. The fibrous type of bar has been sub-divided into two varieties according to whether the process has encroached upon, or drawn up, (1) the urethral, or (2) the vesical surface in its development. They have been shown to be the result of an inflammatory reaction and to be but a part of a generalized chronic interstitial prostatitis.

3. The glandular type has also been sub-divided into two varieties according to whether the hypertrophic process is confined to (3) the posterior prostatic commissure, inside the prostatic capsule

and under the sphincter muscle, in which case a thick, broad bar is formed: or (4) the sub-cervical glands of Albarran, occurring just under the mucous membrane and within the sphincteric ring, and forming what Zuckerkandl has so aptly called "prostatic hypertrophy in miniature," i.e., a small obstructing lobule. Evidences of chronic inflammatory reaction has been the rule likewise in these glandular hypertrophies.

4. Age has not been a differentiating point in any series or type. The youngest of the cases classified as large bars of the fibrous type was fifty-five years of age and the oldest seventy-nine years. In the glandular types the youngest was thirty-six years old and the oldest seventy-three years, though there were three under fifty years of age.

5. The frequency of any special type of bar can best be judged from the number of each type classified as large bars (see also footnote, page 388). There were seven large fibrous bars and eleven glandular. The most frequent single obstructive condition in the entire series was an hypertrophy of the subcervical glands of Albarran.

PLATE 1

Fig. 1. Specimen 3927

Shows the normal bladder cavity, trigone, vesical orifice, urethra, and prostate of a male, dying at the age of forty-two years, as viewed when opened along the ventral or anterior surface. Note size and relative positions of ureteral orifices, trigone, uvula vesicae, urethral trigone, verumontanum, and size of prostate. The proportions are drawn to the scale of $\frac{2}{3}$ of life size, to which all the following illustrations may be compared, as the same scale has been maintained throughout, with the exception of Fig. 3, which is given in life size.

Fig. 2. Median Bar; Fibrous; Type 1. Specimen 3850

F. H., aged sixty-seven years. Entered the Men's Medical Ward on December 21, 1915. Profoundly toxic, catheterization necessary, urinary output small. Died December 27, 1915. Clinical diagnosis: Lobar pneumonia, chronic myocarditis, chronic nephritis. Anatomical diagnosis: Lobar pneumonia, pleurisy, chronic interstitial nephritis, hypertrophy and dilatation of heart. Specimen shows good bar formation; urethral trigone very much shortened with verumontanum drawn up close under the breast of the median bar. Vesical trigone and prostate normal in outline and size. Note the abrupt angle to the normal course of the urethra where the bar occurs. There was likewise a diverticulum in the vertex of the bladder not shown in this illustration.

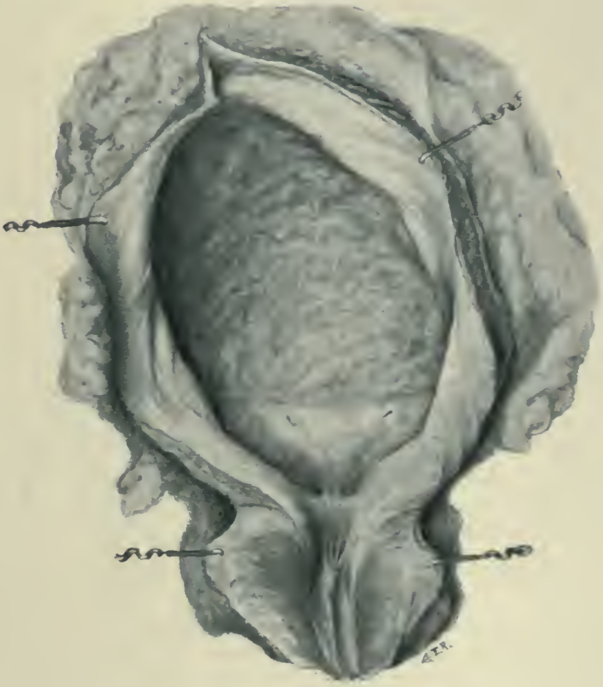

Fig. 1

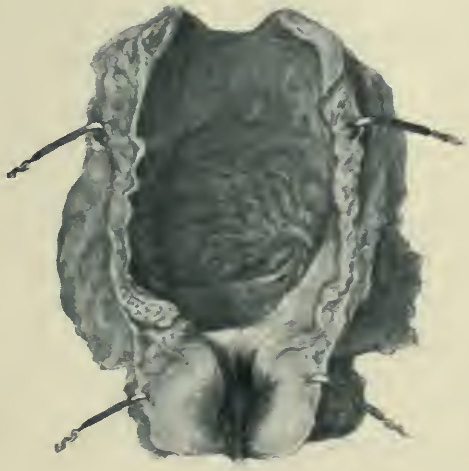

Fig. 2

PLATE 2

Fig. 3. Median Bar; Fibrous; Type 1. Specimen 3850

Same as figure 2, drawn after sagittal section of the specimen, giving in clear detail the position of the bar, character of tissue, location of verumontanum, and abrupt angle to the normal urethral course.

Fig. 4. Median Bar; Fibrous; Type 1. Specimen 3871

M. G., aged sixty. Entered Medical Ward, January 14, 1916. Suffering with an acute attack of influenza. Died January 20, 1916. Clinical diagnosis: Lobular pneumonia. Anatomical diagnosis: Lobular pneumonia, pleurisy, parenchymatous nephritis, early interstitial nephritis. Specimen shows a thick, short bar, with marked shortening of the urethral trigone, verumontanum being drawn up directly under the base of the median bar formation. Prostate of normal size, vesical trigone of the Y-shaped variety. Evidence of urinary obstruction seen in the formation of the small diverticulum in the vertex of the bladder.

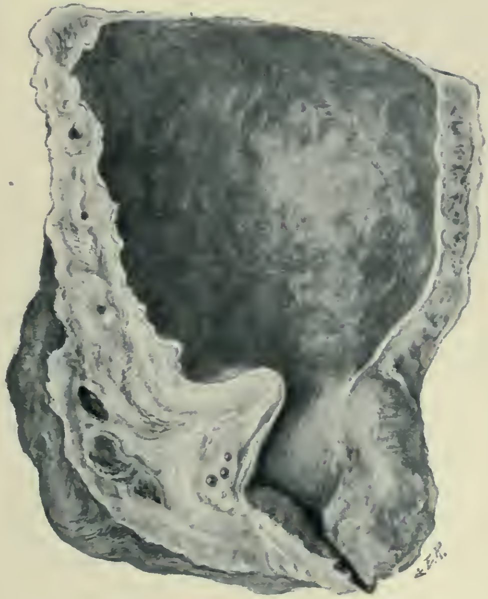

Fig. 3

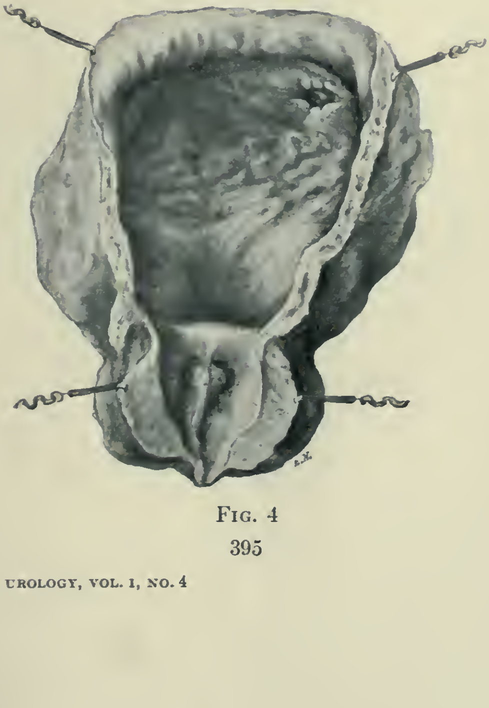

Fig. 4

PLATE 3

Fig. 5. Median Bar; Fibrous; Type 2. Specimen 4164

J. O'H., aged sixty-five. Entered hospital April 31, 1916, as a patient on the Men's Nervous Ward, complaining of right toe-drop. Discharged June 22, 1916. Re-entered hospital, Men's Medical Ward, July 5, 1916, as an indigent patient. Gave history of being a heavy drinker, denied lues, appeared well dedevloped and nourished, had right toe-drop, and a small ulceration on the dorsum of the right hand. Physical examination negative. Genitalia normal, rectal and vesical functions reported "negative." Besides the symptoms of complaint he had a small epigastric hernia, and marked arterio-sclerosis. Wassermann was negative, and urine showed a few leucocytes and epithelial cells in an alkaline medium. Died November 29, 1916. Clinical diagnosis: Cerebral hemorrhage, multiple neuritis, arteriosclerosis. Anatomical diagnosis: Ditto, hypertrophy and dilatation of heart, congestion and oedema of lung, chronic interstitial nephritis. Specimen a beautiful example of fibrous median bar formation, there is no urethral shortening but marked creasing of the trigone and approximation of the ureteral orifices to the vesical orifice; deep bas fond; thinned bladder wall; diverticulum in the vertex of bladder.

Fig. 6. Median Bar; Fibrous; Type 2. Specimen 3834

C. T., aged seventy-six. Entered the hospital July 17, 1914. History highly suggestive of carcinoma of the œsophagus, and after a protracted confinement the patient died December 10, 1915. Clinical diagnosis: Carcinoma of the œsophagus, chronic myocarditis, arteriosclerosis. Anatomical diagnosis: Carcinoma of the œsophagus, stomach and liver; chronic diffuse nephritis. Specimen a good illustration of bar formation and of the second type which is characterized by encroachment on the vesical trigone, with shortening and transverse creasing of it; rather than on the urethral surface. There is a well-marked bas-fond and beginning trabeculation and thinning in the bladder walls. No prostatic enlargement.

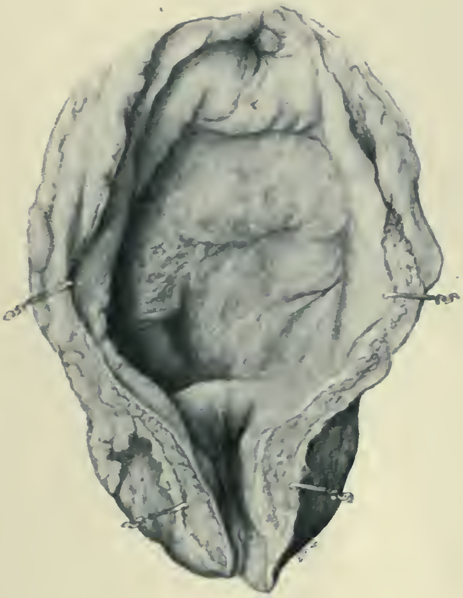

Fig. 5

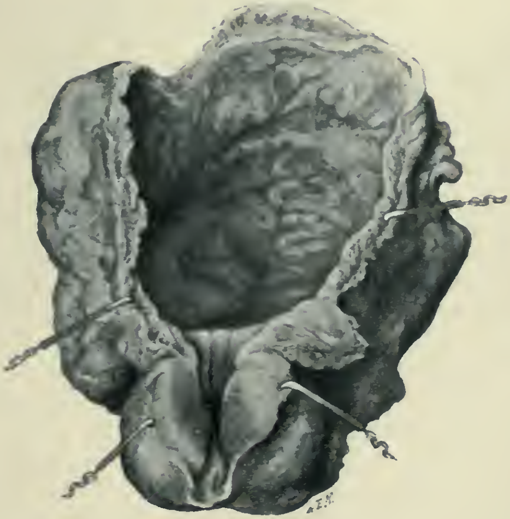

Fig. 6

PLATE 4

Fig. 7. Median Bar; Glandular; Type 3. Specimen 4123

G. F. H., aged fifty-six. Entered the Men's Medical Ward May 17, 1916, complaining of shortness of breath and general cardiac symptoms of eighteen months' duration. History of a specific urethritis in youth. Physical examination reveals general symptoms of broken compensation and Cheyne-Stokes respiration. History notes urinary output as small, urine examination shows low specific gravity, trace of albumin, and a few hyaline casts. Patient died October 1, 1916. Clinical diagnosis: Myocarditis, decompensation, chronic interstitial nephritis. Anatomical diagnosis: General anasarca, dilatation of heart, chronic fibroid myocarditis, multiple pulmonary infarcts, chronic diffuse nephritis. The specimen is one of glandular bar formation due to hypertrophic glandular changes in the posterior prostatic commissure. The bar is thick, rounded, and firm. The bar has an upward tendency of growth causing, as is characteristic of Type 2, a transverse creasing of the vesical trigone; however, grossly, it in no wise resembles a fibrous type of bar. The lateral prostatic lobes are slightly enlarged. The bladder wall decidedly hypertrophied.

Fig. 8. Median Bar; Glandular; Type 3. Specimen 4071

W. I. L., aged twenty-six. Entered the Medical Ward July 14, 1916, with acute pulmonary symptoms. He gave a history of having had a Neisserian infection fifteen years ago. There are no genito-urinary symptoms recorded on the history. He died a typical pulmonary death July 16, 1916. Clinical diagnosis: Lobar pneumonia. Anatomical diagnosis: Lobar pneumonia, cloudy swelling of kidneys. The specimen shows a small bladder with thick (hypertrophied) walls. There is a definite bar at the vesical orifice of the thick glandular type. The hypertrophy of the bladder musculature has been in an effort to overcome the beginning obstruction, and helped by youth the compensation has apparently been complete to the time of death. Section of the bar in the midline demonstrated an increase in the prostatic glandular tissue of the posterior commissure, early hypertrophy at this point having been responsible for the bar formation.

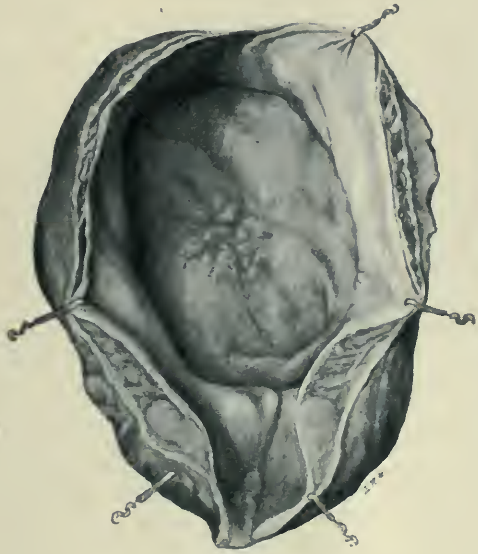

Fig. 7

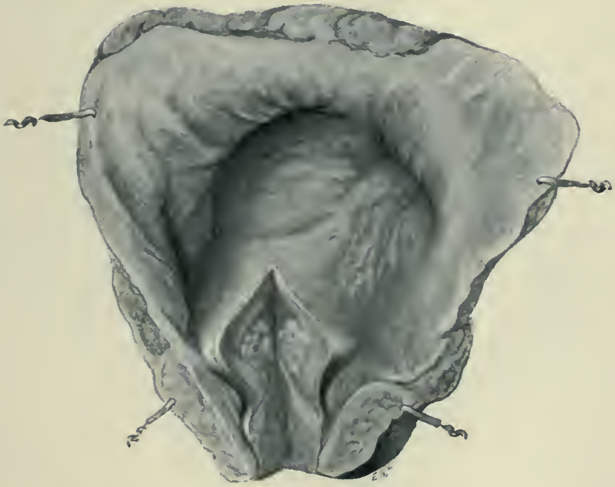

Fig. 8

PLATE 5

Fig. 9. Median Bar; Glandular; Type 3. Specimen 4039

F. K. B., aged fifty. Entered the Neurological Ward, May 30, 1916, complaining of pains in his legs and head, and an unsteady gait. Only genito-urinary note in the history is the occurrence of a specific urethritis six years previously. Patient died in an apoplectic stroke on June 9, 1916. Clinical diagnosis: Cerebral hemorrhage. Anatomical diagnosis: Intracranial tumor, bronchopneumonia, cloudy swelling of kidneys. Specimen is one of the thick median bars which has been incised in the midline to again demonstrate the hypertrophic glandular tissue in the posterior prostatic commissure as the cause of the bar formation. There is a very slight amount of lateral hypertrophy, and the bladder wall is beginning to give way and to dilate, its walls being considerably thinned.

Fig. 10. Median Bar; Glandular; Type 4. Specimen 3963

G. S., aged fifty. Entered the Insane Wards, February 2, 1916. He had been picked up on the street by the police, gave evidence of having lived a tramp's life, could give no coherent statement as to his past and lacked any knowledge of the present. His history notes general lessening of mental faculties, restlessness, senility, and dementia. He is incontinent. Wassermann is negative. Died March 30, 1916. Clinical diagnosis: Senile dementia, arteriosclerosis, dry gangrene of right foot. Anatomical diagnosis: Bronchopneumonia, chronic interstitial nephritis, obliterative arteritis of right posterior tibial artery. Specimen shows a small nodular hypertrophy at the vesical orifice. Behind this is a highly trabeculated bladder wall giving all the necessary evidence of having worked against a gradually increasing degree of obstruction. This nodular hypertrophy is situated just under the mucous membrane, is not associated with any hypertrophy of the prostatic lobes, nor was there any stricture of the urethra present. This type of obstruction is due to an isolated hypertrophy of the subcervical group of glands of Albarran.

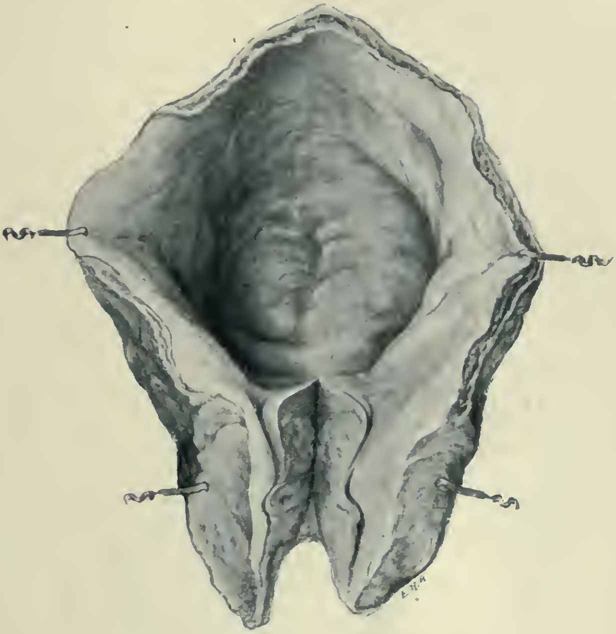

Fig. 9

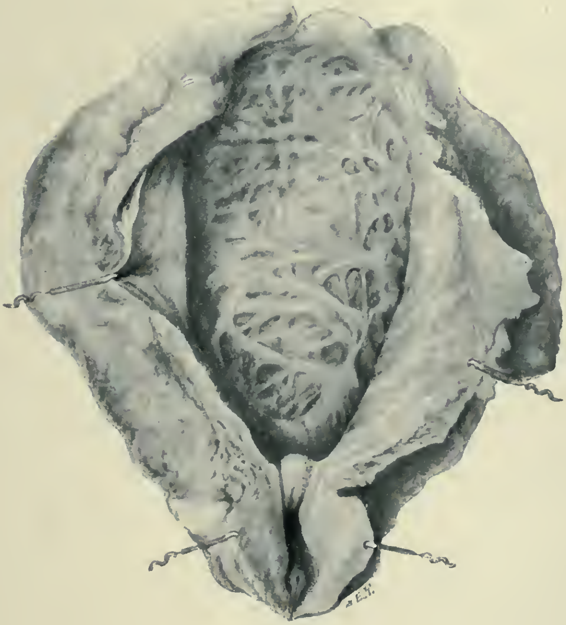

Fig. 10

PLATE 6

FIG. 11. MEDIAN BAR; GLANDULAR; TYPE 4. SPECIMEN 3967

A. B., aged sixty-seven. Entered the Medical Ward, March 20, 1916, complaining of abdominal pain, dizziness, and paralysis of right leg. Patient found to be very weak, pain in abdomen of five days' duration and of shooting character. Inability to use right leg of four days' duration and gradually increasing in its extent. No venereal history. Patient very emaciated, semicomatose, incontinence of urine and fæces. Heart sounds weak, chest negative, abdomen rigid, but with no localizing tenderness. He became progressively weaker and right-sided hemiplegia developed, and he died March 31, 1916. Clinical diagnosis: Cerebral thrombosis. Anatomical diagnosis: Bronchopneumonia, chronic fibrous pleurisy, chronic interstitial myocarditis, chronic valvulitis, arteriosclerosis, chronic interstitial nephritis. Specimen shows a lobular median obstruction with deep lateral cleftings. It is superficial and covered only by the mucous membrane. Bas-fond well developed, bladder walls hypertrophied, prostate normal in size. Like the preceding specimen it represents an isolated hypertrophy of the subcervical glands of Albarran.

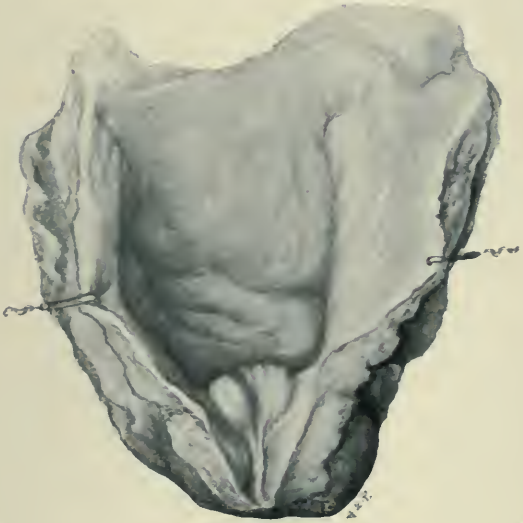

Fig. 11

PRIMARY NON-PAPILLARY CARCINOMA OF THE RENAL PELVIS

HERMAN L. KRETSCHMER

Urologist to Presbyterian Hospital; Genito-Urinary Surgeon to Alexian Brothers Hospital, Chicago, Illinois

The malignant tumors of the kidney pelvis are usually of two varieties—papillary and non-papillary. The papillary are believed to occur, or, at least, are given credit for occurring, more frequently than the non-papillary. Up to 1903, Albarran and Imbert were able to collect only sixteen cases of primary non-papillary carcinoma of the renal pelvis. A careful review of the literature since that time brings the total number of recorded cases up to 43, including my case, reported below.

CASE REPORT

S. R., male, aged 50, referred by Dr. Frank Billings, was admitted to the Presbyterian Hospital, July 29, 1916.

Present complaint. The patient came in for an examination because of an illness which began in the latter part of April, 1916. This came on rather suddenly in the form of a dull aching pain in the left lumbar region, which was relieved by free bowel movements and by hot applications over the belly, but which was made worse by warm water enemas and by lying down. There was blood in the urine coincident with this pain, and blood in the urine has recurred intermittently, sometimes associated with like symptoms in the left back and at times without it. He has noticed no blood in the urine for five weeks. The dull aching pain has been present about half of the time since its first appearance. This has been associated with tenderness on pressure over the left lower rib. He had a poor appetite and was nauseated by food. Since the onset of his trouble, he has lost 18 pounds and his strength and endurance have gradually decreased. His bowels have been constipated for many years.

Previous illnesses. In 1900, the patient had malaria, and in 1912, he had jaundice, which lasted for seven weeks.

Family history. His father, aged 72, is living and well. His mother, aged 67, is living and well. Three brothers and a sister are living and well. One brother died in infancy and one sister was drowned.

Examination. The patient is a rather pale, ill-appearing man. His tonsils are moderate in size and smooth; his throat is irritable; his teeth are in fairly good condition. He has no goiter and no lymph-node enlargements. The heart and lungs are negative. The liver is palpable at end of inspiration and is soft and normal. The lower pole of the right kidney is smooth and slips back into place. The lower pole of the left kidney is smooth and projects about half an inch below the rib. It is twice its normal size and is fixed. It is moderately tender on pressure. The spleen is not palpable. The reflexes are normal.

Rectal examination. The prostate is not enlarged and not hard. The right seminal vesicle is large, soft and tender; the left is not large. There is no infiltration in the intervesicular space.

Urinalysis. Specific gravity, 1020, alkaline, no albumin, sugar, casts or blood.

Blood examination. Red count, 4,300,000; leukocytes, 11,000; hemoglobin, 80 per cent. Blood pressure, systolic, 120; diastolic, 75.

Cystoscopic examination. The bladder is negative, except for the presence of a small median bar. It is impossible to pass a catheter higher than 1 inch up either ureter, although a bougie passes all the way up the left. Five attempts were made to pass a catheter up the ureters and each time an *apparent* obstruction to the passage of the catheter was encountered. An X-ray bougie was passed as high as the kidney pelvis on the left side and an X-ray taken.

Roentgen-ray examination. The roentgenogram was negative for the presence of stones in the urinary tract. It showed the bougie passing into the renal pelvis.

Phenolsulphonephthalein appeared in the urine in nine and one-half minutes. The output for the first half hour was 24 per cent; for the second half hour, 26 per cent; total output, 50 per cent.

The urinary culture showed the presence of long and short chains of Gram-positive streptococci and of Gram-negative bacilli. No tubercle bacilli were found in the urine.

Owing to the fact that the catheters could not be passed up the ureters, it was impossible to carry out pyelography.

Operation. August 19, 1916. Because of the absolute inability to catheterize the right kidney, it was decided to operate on that side first. The usual oblique lumbar incision was made and the presence of the right kidney demonstrated. A kidney normal in size and appearance was found and the wound was closed without drainage. Then the left kidney was exposed by an oblique lumbar incision. The kidney was readily exposed and was found to be about three times its normal size. The pedicle was very thick, hard and infiltrated. The infiltration extended along the large vessels and downward toward the pelvis. With much difficulty the kidney was partially brought up into the wound. A complete delivery of the kidney was not possible, due to the infiltration along the pedicle. In view of the fact that it was impossible to ligate the pedicle in a satisfactory way, two large right-angled clamps were applied to the pedicle and the kidney removed. Iodoform gauze was packed into the wound. Clamps and gauze were removed in thirty-six hours. The patient made an uneventful recovery and was discharged from the hospital on September 11, 1916.

Subsequent course. The patient died February, 1917, six months after operation and ten months after the onset of the first symptoms. As he lived about 200 miles from Chicago, an autopsy was not obtained.

Examination of specimen (fig. 1). The kidney is about three times its normal size. Its consistency is hard and the surface is irregular. On the surface, several white areas are seen. The pelvis feels very hard and solid and is very irregular. There are no areas of fluctuation. The specimen was opened from pole to pole. The most interesting part of the specimen was the pelvis, which was nearly completely filled with a very hard, white, irregular tumor that extended into the ureter, beyond the uretero-pelvic junction. The tumor has grown into the renal parenchyma; in one area the neoplasm can be followed nearly to the cortex. There are no areas of hemorrhage or calcification and no signs of a hydronephrosis.

Microscopic examination. This was carried out by Dr. Burrell O. Raulston, pathologist of Presbyterian Hospital, who reported the tumor to be a *medullary carcinoma.*

ABSTRACTS OF CASES RECORDED IN THE LITERATURE

In view of the fact that these tumors are rare and because of the fact that the reported cases are very scattered, it was thought advisable to collect the case reports, to abstract them briefly and to analyze the cases found. Doubtful cases, in which the author does not definitely state the point of origin of the renal cancer, are not included.

This paper will be limited to a discussion of primary non-papillary carcinoma of the renal pelvis, eliminating from consideration papillary carcinoma of the renal pelvis and carcinomata of the upper end of the ureter.

For instance, Bloch, reporting the operative results of renal tumors from Israel's clinic, cites 126 cases of malignant tumors of the kidney. Six of these he mentioned as being carcinomata. But, unfortunately, no mention is made of the fact as to whether they were primary in the renal parenchyma or in the renal pelvis, and for this reason they are not included in this statistical study.

One case, that of Seenger, is not abstracted and is therefore not included, owing to the fact that the publication was inaccessible.

Albarran

Case 1. Male, aged 37, seventeen months before admission to the hospital, had spontaneous hematuria with discharge of clots and renal colic. Again five months later he had hematuria, preceded by right renal pain, which lasted intermittently for eight days. Since then he has had hematuria once a week, often accompanied by long clots. At examination it was found that the bladder was not bleeding and that the right kidney was enlarged. Nephrectomy was performed and the patient recovered. The kidney was converted into a hydronephrotic sac the size of a large orange and round. On cutting the wall no vestiges of kidney substance could be found. At the level of the ureteral orifice, obstructing it completely, was a nodular tumor the size of a thumb, projecting into the interior of the hydronephrotic sac. The tumor was hard, firm, homogenous and grayish on section.

The histological examination showed it to be an *alveolar carcinoma* with polymorphous cells.

Theodor Bauer

Case 2. Male, aged 69, was admitted June 14, 1908. Early in 1908 he began to have pain in the left upper quadrant of the abdomen, spasmodic in character and radiating toward the shoulder and pelvis. He had spontaneous pain and pain on pressure in the stomach region, left epigastrium and left flank, especially in the left kidney region. The roentgenogram did not show any concrement in the left kidney. The patient died December 9, 1908. At autopsy, the left kidney was found intimately adherent to the surrounding tissues. The walls of the kidney pelvis and calyces were almost entirely infiltrated with tumor tissue, which had passed over into the cellular tissue of the kidney hilus, completely replaced it, and infiltrated the kidney parenchyma. The tumor was grayish white in color. About the middle of the kidney, at the point of greatest convexity of the lateral surface, the tumor had broken through the capsule and involved the surrounding fat. The lumen of the left ureter was filled with thick yellow pus. The mucous membrane of the ureter was nodular and red, the upper 7 cm. were contracted and the wall was infiltrated with tumor tissue. The right kidney showed compensatory enlargement.

There were metastases in the liver, heart, lungs and bones, namely, the seventh rib and second lumbar vertebra.

The microscopic diagnosis was *scirrhous carcinoma.*

Beneke

Case 3. Female, aged 55, had been operated on some years before for stone in the kidney, but as nothing was found, the kidney was replaced. She suffered from severe cystitis, and gradually became emaciated, dying in an exhausted condition. Autopsy revealed a moderate degree of pulmonary tuberculosis and an old mitral stenosis; also a total thrombosis of the inferior vena cava and its branches. The thrombi in the renal veins were simply cicatricial, not cancerous. The right kidney showed a moderate pyelitis and a small stone. The left kidney was firmly adherent to the adrenal and to the spinal column. The cicatricial connective tissue was infiltrated with white cancer nodules. One of the lower and one of the upper thoracic vertebrae were infiltrated with carcinoma and destroyed to such an extent that there was a sharp kyphosis.

Microscopically, this cancer mass, was found to be a *pavement epithelium carcinoma.*

Beneke and Namba

Case 4. Male, aged 45, was admitted December 8, 1909. On May 22, 1909, he was struck in the left kidney by the shaft of a wagon. Shortly afterward he passed bloody urine. Since then he has had continuous pain in the left side. On admission, pus and a few red blood cells were found in the urinary sediment. On the left side a kidney tumor could be felt. The first operation, left nephrotomy, was performed December 18, 1909. The second operation, nephrectomy, was performed in February, 1910. The patient died in April. The liver and lung showed metastases. The bronchial glands were free of carcinoma but showed many giant cell tubercules. The right kidney was apparently normal. At the second operation the capsule was found firmly adherent to the kidney and in some places it could not be separated. The capsule itself was infiltrated with white masses and in some places the transition from it to kidney substance could not be made out. The whole kidney was very hard and grayish white. The kidney substance was decreased in volume. In the kidney pelvis there was an ulcer penetrating deep into the medulla. In the neighborhood of the pelvis were firm white bands of connective tissue. Microscopic examination of the ulcer in the pelvis showed its floor to be made up of necrotic tissue masses infected with cocci. Some parts of the floor of the ulcer were not necrotic and were infiltrated with tumor cells, which lay in a thin zone on the floor of the ulcer and in places passed in thick bands into the medulla. The ulcer in the kidney pelvis was evidently a *carcinomatous* one. The authors believe that the bacilli were very superficial and plainly followed and not preceded the ulceration. There were no foci of inflammatory infection of the kidney substance.

Besenbruch

Case 5. Female, aged 59, was admitted February 27, 1905, because of pain in the abdomen, which began three months previously. She had been losing flesh rapidly for some weeks, had no appetite, urinated frequently and was always constipated. Examination revealed on the left side, a hand's breadth beneath the costal arch, a smooth hard tumor the size of two fists, slightly movable. The lungs were negative. The diagnosis of tumor of the left kidney was made. Transperitoneal nephrectomy was done March 14, 1905. The tumor ruptured and a quarter of a liter of thick yellow pus discharged. It was a picture of pyonephrosis. There were several small abscesses in the upper and lower poles of the kidney. The inner walls of the abscesses showed cauliflower-like efflorescences. The kidney was the size and shape of a nodular cocoanut. The fatty capsule was thick and hard and in some places could not be separated from the fibrous capsule. On section, nothing could be seen of the normal kidney structure. There were a number of cavities of different sizes communicating with each other and with the kidney pelvis, and a connective tissue substance forming the walls of the cavities. The ureter was thickened and hard. Where it left the hard connective tissue that filled the normal place of the hilus, its lumen was filled with crumbling, granular masses. Through its further course it was embedded in firm connective tissue.

The patient was discharged well April 10, 1905. He returned May 28, 1906, very much emaciated. The whole left half of the pelvis was filled with a fluctuating tumor the size of a man's head.

Microscopic examination showed that the mucous membrane of the former kidney pelvis and the cavities in communication with it had undergone *carcinomatous degeneration*. Cancer pearls were found.

V. Blum

Case 6. Male, aged 59, was admitted to Frisch's clinic in Vienna for hematuria which had been present for months. No tumor could be demonstrated and there was no pain. Cystoscopic examination showed that the bleeding came from the left kidney. Nephrectomy was performed. There was a hard infiltration of the upper pole.

Microscopic examination showed a *carcinoma* of the kidney pelvis.

Case 7. An old man, very cachectic, died soon after admission. Autopsy revealed a large tumor of the kidney. The kidney pelvis was filled with a branching phosphate stone.

The tumor proved to be a *pavement epithelioma* of the kidney pelvis.

Cattani

Case 8. Male, aged 63, died April 27, 1871. The clinical history was that of an abdominal tumor, not moving with respiration. There was slight albuminuria, and hematuria preceded by signs of cystitis and pyelitis. A few cancerous cells were found in the urine. At autopsy the kidney and pelvis were found to be twice their normal size. The degeneration began at the origin of the ureter, the tissue of which was thick and ulcerated, and grayish in color, and extended into the pelvis; there was also ulceration of the pelvis and purulent perinephritis. There were no metastases. The right kidney showed nephritis.

The microscopic examination proved it to be a *medullary cancer.*

Gaucher

Case 9. A male, aged 50, had been sick for about six months. Had been in the hospital for a long time because of abdominal pain and digestive disturbances. He vomited frequently, and had alternating diarrhea and constipation. On palpation, a large well-defined nodular abdominal tumor was found, manifestly independent of the stomach. The diagnosis was cancer of the omentum. Death was due to erysipelas. At autopsy, there was found, independent of the generalized cancer of the peritoneum, which had been diagnosed during life, a cancer of the right kidney, which, like the tumor of the peritoneum, was an *encephaloid cancer.* It manifestly originated in the pelvis near the opening of the ureter.

The pancreas had undergone cancerous degeneration of the same nature as that of the kidney and peritoneum. On the lower surface of the liver, there was a small nodule at the point of contact of the upper extremity of the right kidney, formed by propagation.

Giordano

Case 10. Female, aged 57, four years before admission, was suddenly seized with violent pain in the region of the right kidney, which radiated toward the hypogastrium and lumbar region. This was followed by a discharge of turbid urine with an abundant reddish sediment. Subsequently she had several attacks of renal colic followed by passage of bloody urine containing clots. She had pain in the bladder and tenesmus. She was admitted to hospital May 8, 1892. At examination she was found to have pain on both sides, but worse on the right. The urine was tinged with blood. A probable diagnosis of stone in the right kidney was made. Nephrectomy was performed. The excised kidney was about normal in size. There was a lardaceous mass originating in the pelvis and pushing back the kidney substance toward the two poles.

The histologic diagnosis was *primary epithelioma of the pelvis.*

Raymond Grégoire

Case 11. Male, aged 45, had had attacks of nephritis, renal colic and hematuria for ten years. In the past three months a large lumbar tumor had developed. Transperitoneal nephrectomy was done. Microscopic examination showed a *cylindrical epithelioma* of the pelvis, with metastasis in the glands.

B. Grohe

Case 12. Female, aged 60, was admitted February 22, 1900. Her illness began in June, 1899, with frequent pain in the right side. There was loss of appetite and weight. The urine was turbid but never bloody. Two weeks before admission the diagnosis of kidney tumor was made. Nephrectomy was performed February 26; the patient died the next day. The kidney surface was nodular. On section, there was marked hydronephrosis. The opening of the ureter was enveloped in a thick growth of papillary excrescences, which formed a tumor the size of a hazelnut. Directly adjacent to this in the external pelvic tissue was a packet of glands as large as hazelnuts which surrounded and pressed upon the ureter.

Section through the paillary excrescences showed a pronounced *adenocarcinoma.*

Hartmann

Case 13. Male, aged 54, entered the service of Duplay September 21, 1886. At the age of 7 he passed gravel. At irregular intervals, he has had intense renal pain. Two years ago he had hematuria without bladder symptoms, which stopped abruptly in two days. Patient had also a good deal of vomiting. Examination revealed on the left side a large tumor of the hypochondrium, extending to the iliac fossa and umbilical region, round, hard and non-fluctuating. The diagnosis was calculous pyelitis with obstruction of the ureter. Lumbar nephrotomy was performed. A large quantity of pus was evacuated and a calculus removed. Death. At autopsy, the liver and the peritoneum at the level of the upper part of the kidney showed white neoplastic nodules. The left pleura showed a large number of granulations, the largest of which were ulcerated. These could also be seen on the surface of the lung, but not on section. The pelvis of the right kidney contained a yellow calculus. The left kidney formed a mass 18 cm. long. The kidney was only a shell 5 to 7 mm. thick. On its inner surface there were partitions separating the dilated calyces. In the partitions there were vestiges of kidney substance, which disappeared on approaching the pelvis and were replaced by a tissue of grayish fibrous appearance, surrounded by islands of fat. In the pelvis, which had thickened walls, there was a small fragment of calculus. The external surface of the pelvis passed gradually into the indurated fibro-fatty tissue. On section of the pelvis, the appearance was that of grayish fibrous tissue. Its internal surface was irregular, nodular, ulcerated and finely reticulated. The changes extended into the upper part of the ureter.

The histologic diagnosis was *alveolar cancer.*

Case 14. Male, aged 55, had a tumor on the left side. It was accompanied by hematuria, pyuria and fever. Lumbar nephrectomy was performed with good operative result. The patient died later of recurrence.

Microscopic examination showed it to be an *epithelioma* of the pelvis and the kidney had been invaded.

Case 15. Male, aged 46, came for examination in March, 1902. For three years he had had attacks of hematuria, which recently were accompanied by pain and lassitude. Cystoscopic examination showed the blood coming from the left kidney. Nephrectomy was performed March 27, 1902. The lower pole was easily freed. The upper pole was adherent to the diaphragm. April 27, the patient developed a left-sided pleurisy. May 28, he showed a generalized cancer with a bloody pleural effusion of the left side and edema of the left leg. Cancerous nodules developed in the lumbar wound and the patient died June 7, 1902. The upper pole of the kidney was filled with a mass of nodules; the lower part of the kidney appeared normal. The lower part of the pelvis was also normal, but its upper part showed a mass of vegetations.

The microscopic diagnosis of a vegetating *pavement epithelioma* developing from the mucous membrane of the pelvis and calyces was made.

Hedenius and Waldenström

Case 16. Male, aged 79, on admission to hospital showed great emaciation, weakness, slight cough and abundant expectoration. There was a frequent desire to urinate, which he attributed to stones, from which he had suffered for many years. In the region of the left kidney pelvis, an oblong nodular tumor could be felt, which extended to the spinal column and downward to the pelvis. The diagnosis was stone in the kidney pelvis and ureter. No operation was performed and the patient died. At autopsy, the left kidney pelvis was found dilated, and the mucous membrane showed a number of nodules from the size of a hazelnut to that of a walnut. These nodular masses infiltrated the entire wall and extended along the renal artery and vein to the abdominal aorta and vena cava, and from there a little upward, but chiefly downward through the lymphatic glands to the promontory of the sacrum. They also continued downward into the ureter.

The microscopic diagnosis was *primary cancer* of the kidney pelvis and ureter.

Hildebrandt

Case 17. Female, aged 48, for a year had had an abdominal tumor and bloody urine. Examination revealed a hard tumor in the kidney region, adherent to the large intestine and liver and to the inferior vena cava. The tumor was extirpated. The kidney was normal in form, only the curve of the pelvis was lacking. On cut section, two parts could be distinguished—one thickened and infiltrated with connective tissue, the other normal. The kidney pelvis was scarcely visible. Its inner surface was not smooth but covered with many villi and excrescences. The ureter was much dilated and adherent to the kidney, and it was hard and rigid. A thick mass had grown into its lumen from the kidney. The microscopic examination revealed in the renal tissue itself alveoli filled with epithelial cells with oval nuclei. The portion of the tumor surrounding the ureter was firm in some places and soft in others. In this tissue lay clumps of epithelial cells beside one another without intervening tissue. These clumps looked like carcinomatous glands. The parts projecting from the internal surface of the pelvis looked like vascular papillae, the vessels of which were filled with a very typical proliferating epithelium.

This epithelium was *pavement or transitional.* The author thinks this tumor originated in the pelvis and invaded the kidney substance later.

Oscar Israel

Case 18. Female, aged 47, died of a fibropurulent peritonitis, secondary to a purulent infiltration in the region of the left kidney. Autopsy showed the right kidney considerably enlarged. At the lower end there was a cyst filled with yellow fluid. In the adjacent calyx there was a yellowish brown stone. The left kidney was larger than the right. On section pus discharged. There was nothing left of the true kidney parenchyma. The dilated kidney pelvis contained a very large stone and one of the calyces contained another. There was extensive ulceration of the pelvis. Near the stone in the calyx there was a soft whitish mass looking like granulation tissue.

Its structure was alveolar, and there was no doubt but that it was a *medullary carcinoma.*

Kielleuthner

Case 19. Male, aged 44. Sixteen years ago, he noticed for the first time that his urine was bloody. The bleeding lasted three days. He had the symptoms of cystitis and for over three years the urine was turbid. Functional tests showed complete atrophy of the parenchyma of the left kidney. The roentgenograms showed what was interpreted as stone in the kidney and another in the pelvis. Patient had never lost weight up to the time of examination, nine months after operation. Nephrectomy. The whole kidney was transformed into a sac and was of moderate size. The calyces were extraordinarily dilated, the parenchyma reduced to a minimum. The whole kidney pelvis was moderately thickened and yellowish white. *There were no stones in the pelvis.*

Microscopic section showed a chronically inflamed kidney pelvis, whose thickened mucous membrane showed extensive *carcinomatous degeneration.*

Kischensky

Case 20. Female, aged 32, had been sick for a month and a half before admission to the hospital January 6, 1900. She could not walk or stand on account of pain and ankylosis of the right knee. She had pain in the region of the right kidney. A tumor could be felt beneath the ribs, thought to be an enlarged kidney pelvis. The urine contained much pus. No operation. The patient died April 13, 1900. Autopsy revealed a neoplasm of the right knee. The entire right kidney was degenerated, consisting of a neoplasm and a considerable quantity of fat and connective tissue. In the midst of this degenerated tissue, numerous small cavities containing pus were found. From the upper and outer borders of the kidney the new growth had extended to the liver. The right ureter was thickened. The neoplasm was found in the calyx and pelvis of the right kidney and throughout the parenchyma of the kidney, in the liver and in the right knee, involving the lower part of the diaphysis of the femur. The tumor also involved the diaphragm adjacent to the kidney and liver, the peritoneum and the lymph glands.

The neoplasm was a *pavement epithelium cancer.*

Kundrat

Kundrat, in 1891, described this type of tumor at the Medical Society of Vienna. He reported three cases.

Case 21. A kidney from a man of 49, the size of a head and adherent to the spleen. The upper part of the kidney showed dilatation of the calyces. The lower part was transformed into a hard, white neoplasm, from which the characteristic *epithelial pearls* could be expressed. In the calyces there was a branching stone, which was probably the cause of the irritation.

Case 22. In a man of 75, the right kidney was twice as large as normal. There was no dilatation of either pelvis or calyces, but the kidney was so completely degenerated that only traces of it remained. The cancerous pelvis and calyces were retracted and the ureter infiltrated for 4 cm.

Case 23. A man of 56, operated on by Billroth. The kidney was four times as large as normal and was surrounded by a capsule and a very thick fatty capsule. The kidney was almost entirely replaced by the *epidermoidal cancer.* In this case the cancer had extended from the pelvis and calyces to the kidney proper.

Luys, Ameuille and Chenot

Case 24. Female, aged 51. The interesting point about this case is that a renal tumor had developed without giving rise to any symptoms that would lead to a diagnosis. Separation of the urine showed a little purulent urine. Nephrectomy was difficult, on account of adhesions.

Microscopic examination revealed a lobulated *pavement epithelioma,* showing a tendency toward epidermal evolution. The origin was in all probability from some point in the pelvis. Autopsy showed no metastases, except in some of the glands near the *vena* cava.

Martin and Mertz

Case 25. Male, aged 46, forty-eight hours following a fight in August, 1915, had an attack of painless hematuria, which lasted for two days. Then the attacks occurred irregularly for the next three weeks, when he had his first pain, which was not severe. The hematuria continued irregularly and the pain increased in severity. There was also frequency of urination. Palpation revealed tenderness over the lower abdomen in bladder region but no tumor. The urine contained pus and a little albumin. Radiogram showed multiple shadows in region of left kidney. Cystoscopy: Right ureter easily catheterized; urine normal. Left ureter was catheterized only after several attempts and an obstruction high up was found. Urine contained pus, blood and albumin. Phthalein did not appear in forty-five minutes. Pyelography was carried out. A diagnosis of infected hydronephrosis with multiple calculi was made. November 6, 1915, lumbar nephrectomy was performed. The patient was living and well seven months after operation. February 5, 1917, the presence of a tumor mass in the left lower abdomen, with cachexia and every evidence of a recurrence, was reported to the authors by the patient's physician. Section of the kidney longitudinally revealed a tumorous growth, hard, brittle, arising from the pelvis, invading the central portion of the kidney and the region of the opening of the inferior calyx. Nodules of the growth were present on the pelvic wall. The ureter was free.

Microscopic examination proved it to be a *primary alveolar carcinoma* of the pelvis, and the authors concluded it was the result of the calculi.

Jack Mock

Case 26. (Unpublished case given by Professor Albarran to Mock.) Female, aged 23, came in because of hematuria which she had in April, 1902. She has had many attacks since, accompanied by pain in the left lumbar region and frequent and somewhat painful micturition. Nephrectomy was performed November 12, 1908, by Albarran. The right kidney, which had been removed, was very large; the parenchyma of the upper part was normal; all the lower half was neoplastic. There was an enormous tumor in the lower half of the pelvis. The ureter was not invaded but there was a small tumor beside it which seemed to occlude it.

Histologic examination showed it to be an atypical *epithelioma of the pelvis* with cylindrical cells, and with tubes passing down into the deep tissues. The patient was seen in October, 1912, four years after the operation, and she was in good health, having had a child in the meantime.

Oraison

Case 27. Female, aged 50, was married in 1878, at the age of 24. On her wedding journey, she made a misstep in going down stairs and immediately had violent pain in the left lumbar region followed by vomiting and hematuria. She had a recurrence of these attacks occasionally during the next three years. In 1894 she began to have continuous dull pain in the region of the left kidney and she could feel a swelling in that region. The urine became turbid; had frequent desire to urinate and pain at the end of micturition. The author first saw her in July, 1903, when she complained of turbid and vile smelling urine and painful and frequent micturition. The urine showed many leukocytes and various kinds of bacteria. There was a swelling about the size of an adult's head emerging from under the false ribs, extending a little below a line connecting the anterior superior iliac spines and passing inside the median line and backward to the lumbar region. It was rounded and smooth, could be moved slightly forward and laterally, but with great pain. A diagnosis of calculous pyelonephritis was made. The roentgenogram was negative. Nephrotomy was performed November 7, 1904. Incision of the kidney was difficult on account of numerous stones; the largest weighed 107 grams. The cavity containing this stone had smooth walls, but a finger was passed through its anterior wall into another cavity containing four more stones, which proved to be in the kidney pelvis. Its walls were not smooth, but irregular and very hard, giving the sensation of a vegetating epithelioma of the uterus. In this cavity there was a small quantity of infected pus. The patient died three days after operation.

Microscopic examination of the fragments of tumor removed at operation showed that the greater part of the specimen was made of neoplastic tissue. The tumor *developed from the stratified pavement epithelium* of the kidney pelvis.

Rudolf Paschkis

Case 28. Male, aged 47. At the age of 8 he had urinary retention, caused by a stone. Hematuria began four or five months before admission, since which time he has had several attacks. On bimanual examination, a small hard nodular tumor, about the size of an apple and somewhat sensitive to pressure, was found in the region of the right kidney. Ureteral catheterization revealed a few drops of turbid alkaline urine, with a moderate amount of blood and a few pus cells. Nephrectomy was performed. The kidney pelvis was dilated to more than the size of a fist and thickened. In the kidney pelvis, there were necrotic, freely movable masses, from the size of a hazelnut to walnut, friable, and reddish brown in color. In the wall of the kidney pelvis, at the lower pole, there was a sharply circumscribed tumor about the size of a 5 mark piece.

Microscopic examination proved it to be a case of *cylinder cell carcinoma,* solid in structure in some parts and in others showing a tendency to lumen formation and secretion.

Porter

Case 29. Male, aged 69. At the age of 22 he had an attack of ureteral colic. In 1909, patient had hematuria. March 29, 1909, he commenced complaining of pain in chest, abdomen, legs and back, especially severe in left side. Pressure over the left kidney caused pain. Some enlargement of the kidney was apparent. Urine contained albumin, no casts, many pus and red blood cells, a few kidney cells, much mucus, many proteus bacilli and numerous streptococci. First operation, lumbar nephrotomy, April 1, 1909; there was found a hydronephrosis and two stones were removed. At the second operation, July 28, 1909, the old wound was enlarged, and two large and several small stones were removed. At the third operation, September 28, 1909, the kidney, with the upper three-fourths of the ureter, was removed. The inner surface of the pelvis of the kidney was occupied in part by what appeared to the unaided eye to be masses of granulation tissue. Microscopic examination showed them to be *carcinomatous.* The patient died December 19, 1909, nine months after the first operation.

Rayer

Case 30. A female, aged 58, died after attacks of abdominal pain and hematuria. Autopsy was performed thirty hours after death. Many cancerous nodules, ranging from the size of a hazelnut to that of a partridge's egg, so numerous they could not be counted, were found in the liver. The substance of the kidney was normal, but on the internal surface of the membrane of the pelvis there were numerous small pedunculated tumors, evidently formed of fibrous tissue infiltrated with *encephaloid* matter. There was a similar alteration in the ureters. There was a cancerous mass formed by the agglomeration of small tumors, similar to those described previously, round and encrusted with calcareous concretions in the fundus of the bladder.

Otto Retzlaff

Case 31. Male, aged 43, was admitted February 10, 1903. In July, 1902, he had had a strain in lifting a heavy load and had pain in the left side. Lost his appetite and became emaciated. At the end of August developed hematuria for three or four days, and also for a day in September. After that the urine was always turbid and he had frequent desire to urinate. Since September, 1902, has had pain in the left side radiating to the testicle. On examination, pain and dullness is elicited a hand's breadth below the left costal arch. In the left supraclavicular fossa there was a small hard gland. February 20 a laparotomy was performed. A hard nodular tumor of the left kidney, with numerous metastases, was found. Because of the size of the tumor and the adhesions, operations was considered impossible. Patient died February 22.

Autopsy showed a tumor mass firmly adherent to the lumbar muscles. It had also penetrated the spleen and some nodules were visible in the tail of the pancreas. The fat capsule of the kidney seemed to be replaced by the tumor mass. There were extensive adhesions to other organs. On section, almost nothing could be seen of the kidney substance, nor was the kidney pelvis recognizable as such, but its place was filled up with a grayish tumor mass.

Microscopic examination showed an alveolar tumor with a connective tissue stroma and the alveoli filled with cells. Pavement epithelium cells prevailed. This was undoubtedly a *pavement epithelium carcinoma*, and it is highly probable that it originated in the kidney pelvis. It then infiltrated the kidney and produced metastases in various organs, all of which showed the pavement epithelium type.

Case 32. Female, aged 54. The predominating symptoms were those of stomach distress and a gastro-enterostomy was performed July 2, 1902. She died July 7, 1902. The right kidney was a round hard body almost the size of a fist, surrounded by abundant fat. On section, it was found so thoroughly infiltrated with a white tumor mass that it was hard to recognize it as a kidney. The pelvis on the side toward the ureter was thin walled. Toward the kidney there was a diffuse thickening, caused by the tumor mass. The kidney pelvis was thickened.

Microscopic examination showed a *medullary carcinoma* with a very scanty stroma.

Ignazio Scalone

Case 33. Male, aged 39. At the age of 31 he began to notice a change in the urine; it became more abundant and slimy. At 33 he began to have mild attacks of pain over the right costal arch. In 1908, he had two attacks of hematuria, after which he had fever and discrete pain in the kidney region, radiating to the bladder. Ureteral catheterization demonstrated mucopus in the right kidney. The whole lumbo-hypochondriac region showed a swelling on the right side. On the side of the tumor the veins of the spermatic plexus were varicose. Under the microscope many pus corpuscles were found in the urine. Nephrotomy was performed. On opening what appeared be the cavity of the pelvis, many small calculi were found. The cavity of the pelvis was increased by distention of the renal parenchyma and looked as if it were filled with a villous cancer. The patient died. No autopsy.

Histologic study of the tumor was made from the numerous pieces removed at operation. The author concludes that it was an *epidermoid flat pavement epithelioma* of the kidney pelvis, extending to the cortex of the kidney.

Scheel

Case 34. Male, aged 37. Six weeks before admission, he had boring pain, beginning in the lumbar region and radiating to the umbilicus. He lost appetite and became emaciated. The urine was turbid. The right kidney region was sensitive to pressure but no tumor was felt. A few days later he complained of sensitiveness in the midline above the umbilicus. A tumor was felt, apparently above the pancreas. Exploratory laparotomy was performed. The great omentum contained tumors and there was a tumor, the size of a walnut, in the neighborhood of the head of the pancreas. Examination of a piece of the omental tumor showed pavement epithelioma. The patient died from pneumonia after attempting suicide four weeks after operation.

Macroscopic examination showed that there was a tumor, partly solid and partly papillary, of the kidney and kidney pelvis with metastases along the kidney and large abdominal blood vessels, in the omentum, right adrenal, the liver, the diaphragm and the lungs.

Microscopic examination showed that the tumor consisted of two sharply defined, absolutely different parts—*a pavement epithelioma in the kidney tissue and a cylindrical epithelioma in the kidney pelvis.*

Schievelbein

Case 35. Male, aged 44, had been sick for ten weeks with pain on the right side below the costal margin. He had loss of appetite, rise of temperature, weakness and rapid emaciation. In the right hypochondrium a slight resistance could be felt, painful on pressure. At the level of the seventh cervical vertebra a hard tumor, the size of an apple, could be felt. This examination was made October 10. On October 12 slight paralysis of the lower limbs developed, accompanied by decrease in sensation. Patient died October 22.

Autopsy showed a tumor of the sixth cervical vertebra, exerting pressure on the spinal cord. The right suprarenal was enlarged, showing nodules. In the fibrous and fatty capsule of the kidney were numerous nodules. The right kidney was enlarged. On section the upper half was found filled with circumscribed nodules, ranging in size from that of a pea to a cherry. These were grouped about a point in the kidney pelvis where there was an irregular ulcer about the size of a five pfennig piece, with a rough, reddish-white base and slightly raised edges. The mucous membrane of the rest of the kidney pelvis was grayish-rosé color, smooth and not dilated.

Microscopic examination showed a *primary cancer* of the kidney pelvis.

Spiess

Case 36. Female, aged 54, for years had had the symptoms of a left sided pyelitis—pain in the left kidney region, pus in the urine, from a colon infection, but no hematuria. More recently the pains have increased and the patient has become emaciated. Examination in April, 1912, revealed cystitis; the right kidney functioned normally, while from the left ureter no urine was obtained. A diagnosis of tumor was made.

At operation the left kidney pelvis was found much enlarged, and contained a calculus and a firm, non-papillary tumor. The regional glands were not involved. Nephrectomy was done. Operative recovery was good. In December, 1912, there was considerable abdominal pain, radiating into the left leg, and large tumors were found along the vertebral column.

Macroscopically, the specimen was a much enlarged kidney with capsule. On section, the markings were quite distinct. The kidney pelvis was somewhat enlarged, but surrounded by very little fat. The mucous membrane was grayish white in color, somewhat granulated and hypertrophied, and lying in ridges. At the lower end of the pelvis, about 1 cm. above the ureter, there was a round tumor of a firm consistency and sharp outline. The surface was granular. On section the tissue was found to be grayish white, slightly granular, with a light opaque juice. In the pelvis there was a hard, brown, mulberry-like oxalate of lime stone.

Microscopic diagnosis. *Squamous epithelioma.*

Stüsser

Case 37. Female, aged 66, had always been well until a few weeks before admission, when she noticed a swelling on the left side. The tumor increased slowly but continuously. The urine became dark and turbid. A diagnosis of cystic ovarian tumor was made. Operation September 30, 1909. The tumor was found to be a hydronephrotic kidney. Nephrectomy was performed. Macroscopically the specimen was a typical picture of hydronephrosis. The lower pole of the kidney was preserved, but most of the kidney went to form the wall of the sac. The pelvis was dilated to the size of a man's head and was very thin at the places where it was free of tumor. There were tumors in its walls separated by a small furrow representing the mouth of the ureter.

Microscopic examination showed the presence of a *pavement epithelioma.* The thickened and hardened mucous membrane of the pelvis showed that carcinoma cells had caused the thickening. Later she began to have pain in the pelvis and legs. A tumor could be felt on the left side below the lower rib and ilium. Below the trochanter major a hard nodular non-fluctuating tumor could be felt on the bone. By the beginning of October, the tumor in the lumbar region was as large as a fist. The patient died November 4.

Autopsy revealed a chain of carcinomatous lymph glands along the vena cava. On the left side of the first and second lumbar vertebrae, there was tumor the size of a fist which had partially eroded the vertebrae. There was a firm nodular tumor on the trochanter major of the left femur. The liver showed nodules of various sizes.

Domenico Taddei

Case 38. Male, aged 40, entered the clinic March 20, 1905. His illness began twenty-seven months before with sudden pain in the right hypochondrium, radiating toward the scrotum. In September, the attacks became more violent and the urine was bloody. He was sent to the surgical clinic with a diagnosis of pyonephrosis. Examination revealed an ill-defined swelling in the right hypochondrium. March 28, nephrectomy was performed. There was difficulty in isolating the kidney, because of the adhesions, especially in the region of the pelvis. The third day anuria developed, also stubborn vomiting, slow and rapid pulse, and the patient died.

At autopsy the form of the kidney was found to be well preserved, except for an irregular increase in size in the region of the pelvis. On section the peripheral part of the kidney showed several cavities containing pus. The neoplastic mass compressed the vena cava and occluded its lumen. The tumor also occluded about 5 cm. of the ureter. The neoplastic occlusion of the vena cava had caused a thrombosis, which extended on the left to the iliac and on the right to the popliteal vein. Bacteriological examination of the pus from the cavity in the kidney showed Fraenkel's diplococci.

Microscopic examination showed a typical *pavement epithelioma* of the renal pelvis.

Tuffier

Case 39. Male, aged 65, had had hematuria continuously for three months, associated with pain and a sensation of weight on the right side for about a month. In the right lumbar region a large, smooth, hard tumor was palpable, which disappeared under the ribs and extended downward to a point halfway between the umbilicus and symphysis.

Lumbar nephrectomy was performed. The kidney presented an enormous hydronephrosis, being about twice its normal size. In the region of the hilus there was a tumor-like hardening, which, on incision, discharged a large amount of very dark blood. In the kidney pelvis could be felt a hard infiltration, the size of a nut.

Microscopic examination revealed strands of epithelial tubules in the connective tissue; the cells were *cylindrical;* the centers of some were necrotic. There were also some of these tumor cells in the lumen of the arteries and in the thickened wall of the kidney pelvis. Eight weeks later the patient died of bronchopneumonia.

At autopsy the right kidney was found replaced by large masses of firm connective tissue, in which the ureter had been lost. A few white cancerous nodules were found in the liver.

Verhoogen

Case 40. Female, aged 56, in August, 1897, began to suffer from frequent urination and pyuria. The right kidney was very large. The urine from the left ureter was clear. Operation, October 26, nephrectomy. The patient died the next day. On opening the kidney, an abundant creamy pus was discharged. On introducing a finger into the cavity, the pelvis was found to be filled with a hard tumor, the size of a large egg, and *scirrhous* in appearance. The lower part of the concave border of the kidney was also invaded by a *cancerous* tumor the size of an apple.

Wehr

Case 41. Female, aged 53, suffered from pain in the renal region for five months. She had acute bladder pain at the same time, and hematuria for the last four months. On examination a large renal tumor was found, which extended from the ribs to the crest of the ilium. Lumbar nephrectomy was performed and the patient died. It was found that the tumor originated in the pelvis and infiltrated the kidney. *It was a carcinomatous sarcoma.* At autopsy, generalization in the pleura was found.

Wilson

In a series of 92 cases, Wilson found 4 renal carcinomata, taking their origin from the collecting tubules. One of these 4, he says, was a tumor of the renal pelvis apparently of embryonic origin (case 42). It was a squamous-celled *epithelioma*, resembling histologically a cancer of the lip and evidently derived from the ectoderm.

ETIOLOGY

Nothing definite is known with reference to the etiology of carcinoma of the renal pelvis. Predisposing factors, such as the rôle played by stone and metaplasia, will be considered further on.

An analysis of the 43 cases collected, including the case reported in this paper, shows that 26 occurred in males and 16 in females. In Wilson's case the sex was not mentioned. According to these figures, there does not seem to be any great preponderance of one sex over the other, nor does one side seem more prone to the development of this disease than the other, for in this series it was found that 16 cases occurred on the right side and 18 on the left. In the remainder the side on which the lesion occurred was not mentioned. The right kidney, being more movable than the left, is said to be more prone to develop certain renal diseases, such as, for example, tuberculosis, but such, apparently, is not the case with this disease.

In only two cases was there a definite history of trauma, those reported by Beneke and Namba, and by Retzlaff.

THE RÔLE PLAYED BY CALCULI

In 11 cases, there was found, associated with the tumor, renal stones. In two cases, not only was the calculus present on the side of the tumor, but calculi were also present on the opposite side (Hartmann and Israel). In one case, that of Beneke, a stone was found in the well kidney, while the diseased kidney had none.

It is believed that gall-stones predispose to the formation of cancer in the gall-bladder. This fact has been repeatedly advanced as a possible factor in the production of cancer of the kidney pelvis. While this might possibly be called upon to explain the occurrence of cancer in the cases in which stones are found, it cannot be considered the predisposing factor in those cases in which no stones were found, which numbered 32, assuming, of course, that if stones were present the author would most certainly have mentioned that fact. It may well be within the bounds of possibility that the stones were secondary to the tumor formation.

Thus, Israel believes that stone had something to do with the formation of the carcinoma in his case, for he says,

> The stone in the kidney pelvis was probably responsible for the hydronephrosis, and later, together with the smaller stones, for the ulceration. It is hard to say how much the hydronephrosis had to do with the development of the carcinoma, but it is probable that the stone, which lay near the origin of the tumor, had a part in its formation, as experience has shown that continuous irritation may lead to cancer production.

Kielleuthner thinks that the calculi are the primary factor in causing the inflammation, and that the course is somewhat as follows: inflammation, scar formation and finally pyonephrosis. The tumor arises secondarily in the chronically inflamed mucosa. In his case there was no xerosis as a connecting link between the normal epithelium and the tumor, but there was an epithelium developed to many times its normal thickness and it looked as if the thickened epithelium had undergone a slow transformation into carcinoma.

Paschkis, in reporting his case, makes the statement that it is impossible to say whether the anuria and the stone discharged years before had anything to do with the development of the tumor; but it is possible, as stones have been held responsible for the development of kidney tumors.

Hartmann also calls attention to the fact that his case followed a calculous pyelitis, and that the changes in the pelvis were analogous to the cancerous changes sometimes found in the gall-bladder following gall-stones.

Oraison is disposed to accept the hypothesis that the tumor was caused by irritation, and the probable order of lesions was lithiasis, pyelonephritis, hypertrophy of the kidney and epitheliomatous degeneration of the pelvis.

Rokitansky, in 1861, pointed out the possibility of the transformation of the epithelium of the renal pelvis, a condition usually designated as metaplasia or leukoplakia. Since then leukoplakia of the urinary tract has been studied by many writers, namely, Weichselbaum, Kauffmann, Dittel, Posner, Baraban, Hallé and others. Leukoplakia may involve the entire urinary tract, kidney pelves, ureters, and bladder, or it may be localized in the pelvis and ureters without involving the bladder. Cases of leukoplakia of the urinary organs have been reported by Orth, Chiari, Caselin and others.

Hallé, who has studied this condition rather carefully, calls attention to the frequent coincidence of leukoplakia and calculi. The author thinks, however, that the mechanical irritation of the calculi is not a direct cause of the leukoplakia. The primary cause is chronic inflammation, and the mechanical irritation plays only a secondary part in aiding the epithelial changes. In two of Hallé's cases there was present both tuberculosis and leukoplakia, and he believes that the tuberculosis was secondary.

Albarran likewise calls attention to the fact that the epithelium of the renal pelvis can become transformed into pavement epithelium analogous to that of the skin. He believes that the only etiological factor worthy of note is the possible coexistence of calculi of the pelvis and epithelial tumors of the pelvis. He believes that the stones, by chronic irritation, may produce leukoplakia and the leukoplakia may be the first stage in the development of a true epithelioma.

Bauer states that the appearance of typical stratified pavement epithelium in the urinary tract and its tumors is a well known fact and is explained by metaplasia. He suggests the possibility, in his case, of its having been caused by stone formation followed by pyelitis.

Schievelbein believes that the cancer in his case must have been due to a metaplasia of the transition epithelium of the kidney pelvis.

Stüsser says that the unexplained point in such tumors is the cornification of the transition epithelium of the kidney pelvis. Metaplasia is much less freely used in explanation of this phenomenon recently than it formerly was, as it is considered now that only very closely related forms of cells may pass over into one another; nor is the hypothesis of displaced embryonic cells very satisfactory. He thinks that Ribbert's explanation is more satisfactory, which is as follows:

> "It is quite conceivable that transitional epithelium may assume the qualifications of epidermis under certain circumstances to a much greater extent than it ordinarily does. It is conceivable that even in the embryo there may be a greater extension of pavement epithelium upward from the Wolffian duct, and that this explains those cases in which greater or less areas in the pelvis and ureter are found covered with epidermis, and those cases in which tumors develop from these sections of the urinary tract showing the same kind of epithelium."

According to Taddei, the observation of tumors developed in the bladder on plaques of leukoplakia and the observation of foci of leukoplakia in the pelvis, which, however, is rarer than leukoplakia of the bladder, and the metaplasia of the epithelium of the pelvis observed in the case of Kitchenski, seem to confirm the idea that these pavement cell cancers are due to epitheliomatous transformation of plaques of leukoplakia, in which, moreover, we can observe histologically the change of the epithelium of the pelvis into stratified pavement epithelium. The origin of these plaques of leukoplakia is generally attributed to a chronic irritation of the epithelium, sometimes easily accounted for by the presence of stones but more generally unknown. In considering the rôle played by stones, he states that they may be a factor in the formation of tumors, either directly or indirectly by producing leukoplakia, but it is possible in some cases, at least, that the calculi are secondary and are due to the urinary retention.

Scheel's case is interesting because there was present beside the cancer a papilloma. He states that the tumor must have had its origin from metaplasia of the transitional epithelium.

He further states that it has never been definitely proved that normal epithelium can undergo a true metaplasia, and even if it can, there must be some predisposition in the cells to such a change in order to explain why mechanical injury does not always cause metaplasia, and why metaplasia is occasionally observed without any history of mechanical injury. In his case there was no history of any lesion that could have caused the metaplasia. He comes to the conclusion that he must attribute the metaplasia, as well as the carcinoma and the papilloma, to an abnormal predisposition in the epithelial cells themselves.

Scalone comes to the conclusion that his case of epithelioma of the kidney was probably due to leukoplakia of the pelvis, complicated by calculi and colon bacillus infection.

Grohe's case was an adenocarcinoma, which he believes originated from the tubular glands of the kidney pelvis and infiltrated the pelvis, calyces, fibrous capsules and the kidney itself.

Wehr's case is remarkable in that it is the only case of mixed tumor found in this series. His was a case of carcinomatous sarcoma, originating in the pelvis and infiltrating the kidney.

SYMPTOMATOLOGY

Hematuria is one of the most important symptoms of tumors of the kidney pelvis. Very often it is the only symptom that brings the patient to the physician. The hematuria usually is painless, without any history of trauma and without the production of symptoms. Because of these characteristics, not much stress is laid on the presence of blood in the urine, so that when many of these patients finally come in, the chances of a radical cure are out of the question. Hematuria was present in 24 cases of this series. The length of time which the hematuria was present varied considerably; in some it was noted for four, six and ten years, in others for a number of months or weeks or days. In one case the hematuria occurred sixteen years ago, and in this instance it doubtless had nothing to do with the occurrence of the tumor, for it would be difficult to see how a patient could have a tumor of this kind for that length of time.

Pyuria. It is usually believed that tumors of the kidney do not show the presence of pus in the urine. That this clinical teaching is an error has been proved by a few of these 43 cases, for pus was found in the urine in 13 of them. Not only was pus found in the urine in these cases, but a pyonephrosis was demonstrated at autopsy in 5 cases. There was also a hydronephrosis in 8 cases. In one case there was a hematonephrosis.

Gastric symptoms have, as a rule, been very rare. In this series they were noted in but 3 or 4 cases. Gaucher's patient complained of abdominal pain and digestive disturbances. One of Hartmann's patients complained of vomiting and one of Retzlaff's of severe gastric distress. My own patient had nausea after food intake and had a poor appetite.

A palpable tumor was found in 14 cases.

The occurrence of metastases. It is a rather striking fact that of the small number of cases which forms the basis of this report, a review shows that autopsies were carried out in 19 cases. The autopsy reports show that metastases were found in the following organs: In the liver in 8 cases, the peritoneum in 3 cases, the lungs and pleura in 5 cases, and the pancreas, heart, spleen, blood vessels, adrenal, omentum, diaphragm and various glands in isolated cases. Of more than passing interest are the cases of Beneke, Schievelbein and Stüsser, in which metastases were found in the osseous system. Hypernephromata, as is well known, have a tendency to produce bone metastases. I am not familiar with any statements relative to this fact regarding non-papillary tumors of the renal pelvis, yet in this small number of cases there were 5 in which bone metastases were found; in the femur in the case of Stüsser, and in some of the vertebrae in the cases of Beneke, Schievelbein, Bauer and Spiess.

Involvement of the ureter was mentioned in 9 cases. In some the involvement was for but a short distance, and in others for longer distances; in one the changes were noted for 7 cm.

DIAGNOSIS

In order to be of help to patients suffering from this malady, it is essential that the diagnosis be made early and that operative treatment be instituted at once. It will probably be difficult to make an accurate diagnosis as to whether the tumor is primary in the kidney or in the kidney pelvis, so that the diagnosis primarily must be that of tumor of the kidney. In the cases in which the diagnosis can be made by palpation, one may be justified in assuming that these cases are probably beyond our reach. In order to make an early diagnosis, one should resort to all methods of diagnosis, namely, the roentgen-ray, pyelograms and functional kidney tests, besides the usual general physical examination.

Whether or not pyelograms will aid in making an early diagnosis has not been proved. Reasoning by analogy, I think one is justified in making the statement that the pyelogram is probably the best single agent at our command by which a diagnosis can be established. Pyelograms were mentioned as having been made in only one case in this series, that of Martin and Mertz. In my case, as can be seen by a review of the clinical history, many attempts were made to catheterize the ureters, and each attempt was a failure. Our object in trying to catheterize the ureters was to perform pyelography. While the pyelogram aids us in making the diagnosis of kidney tumor, it probably will not aid much in differentiating the tumor, whether renal or pelvic in origin. The diagnosis may be complicated by the presence of renal calculi, so that one may be inclined, because of the presence of the shadows in the roentgenogram, to diagnose stones and miss the tumor.

The diagnoses as given in these 43 cases varied considerably, and were as follows: in 11 pavement epithelioma, in 3 alveolar carcinoma, in 2 scirrhous carcinoma, in 4 medullary cancer, in 2 an encephaloid cancer, in 3 cylindrical epithelioma, in 2 squamous-celled epithelioma, in 2 primary cancer, in 4 epithelioma, in 1 epidermoidal cancer, in 6 there was carcinomatous degeneration, 1 was an adenocarcinoma, 1 a carcinomatous sarcoma, and in 1 there was a pavement epithelioma of the kidney tissue and a cylindrical epithelioma of the kidney pelvis.

PROGNOSIS

The prognosis in these cases is extremely bad. The immediate or operative mortality has been very high. Of the 43 cases here collected, 30 were operated on, 10 were not operated on and in 3 nothing was said about operation. Of the number operated on, 16 died immediately or soon after the operation, so that the operative mortality in this series must be placed at 53.3 per cent. Nor is the prognosis very good as regards an ultimate cure. In my case, the patient lived six months after the operation. The average duration of life, as compiled from this series, in the cases in which the fact was mentioned, has been seven months and fifteen days. The longest case on record, as far as I know, is that of Albarran, reported by Mock, in which the patient lived four vears after the kidney was removed.

TREATMENT

The treatment of this type of tumor does not differ from the treatment of other malignant renal tumors. Nothing short of an immediate nephrectomy should be done as soon as the diagnosis is made. Of the 30 cases in this series that were operated on, nephrectomy was performed in 21; of this number, 9 died, 4 recovered, and in 7 the result was not stated. Nephrotomy was performed in 3 cases, of which 2 died and in the third the result was not stated. In two cases, both operations were performed; in two others exploratory laporatomy was performed and in one a gastro-enterostomy; all of these patients died after operation. In the twenty-eighth case the type of operation was not mentioned.

CONCLUSIONS

1. Non-papillary tumors of the renal pelvis are very rare.
2. The diagnosis is made late in the course of the disease, generally too late to give the patients much hope for a cure.

3. Doubtless more of the tumors will be recognized early due to the advances in diagnostic measures and to the more universal use of the cystoscope in all cases of urinary hemorrhage.

4. The prognosis is always very grave.

5. The operative mortality is very high and the duration of life after operation in suçcessfully operated cases is very short.

6. The presence of pus in the urine does not exclude renal tumor.

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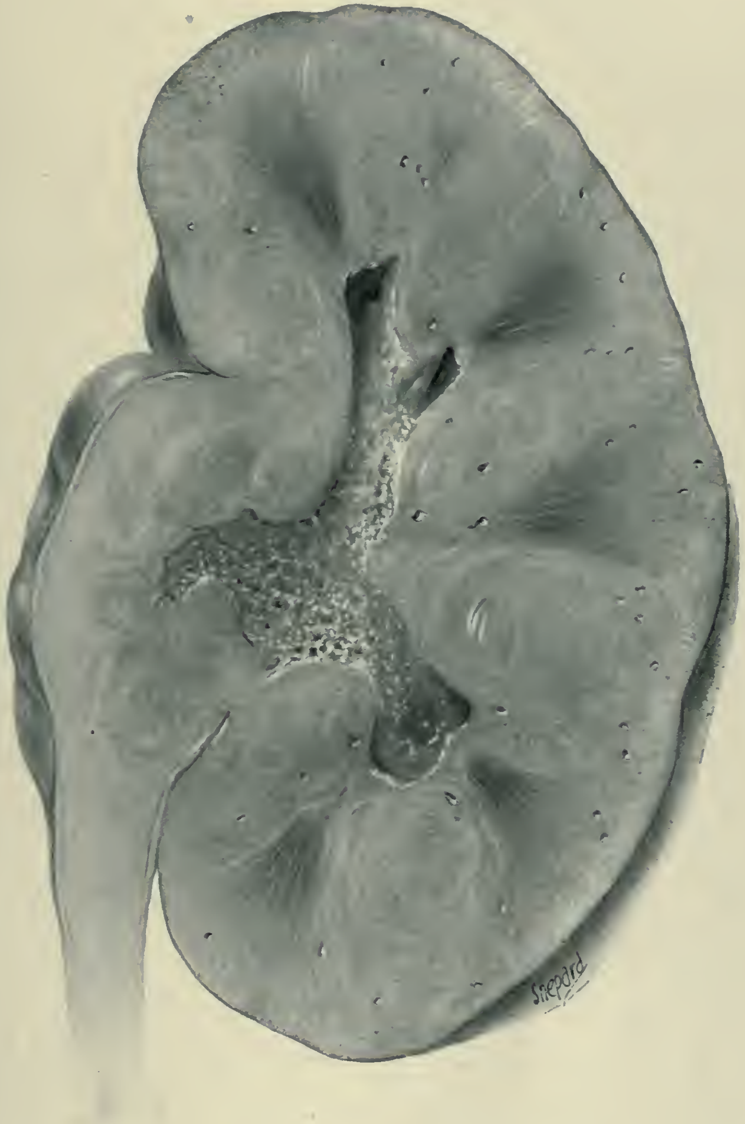
PLATE 1

Fig. 1. Carcinoma of Renal Pelvis

NON-PAPILLARY CARCINOMA OF THE RENAL PELVIS PLATE 1
HERMAN L. KRETSCHMER



DIVERTICULUM OF THE BLADDER

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Many cases of vesical diverticula have been reported within recent years and a large literature dealing with their etiology and treatment has developed. In former days the condition was frequently overlooked and an absolute diagnosis was possible only by exploratory operation. With the development of the cystoscope the diagnosis was made certain and much information regarding their size and shape learned by the employment of the X-ray.

Concerning the etiology of the condition much has been written and most authorities agree upon the classification dividing them into congenital and acquired. English (1) inclines to the view that the elements composing the diverticulum determine the class to which it belongs: that the congenital variety has muscular coats while the acquired form consists solely of mucosa. I am inclined to agree with Lower (2) that the division is an artificial one and that in reality all diverticula are acquired, being brought about by one factor, namely urinary obstruction. Thomas (3) has gone very carefully into a review of the literature concerning the embryology and etiology of diverticulum and those interested in the various views of the subject may refer to this paper.

Diverticula vary greatly in size, ranging from very small outpouchings to sacs larger than the bladder itself. Since any condition resulting in urinary retention invites infection, it is not unusual to find marked grades of inflammation present. Calculus formation frequently complicates the condition and these are not infrequently present in the sac itself. The more conservative procedures such as catheterization, bladder irrigations, etc., frequently fail in the prevention of calculus-formation and it is impossible to clear up the infection unless the diverticulum and its cause are radically removed.

DIAGNOSIS

Diverticula are usually discovered during the routine cystoscopic examination. At times it is suspected and the suspicion is frequently confirmed following catheterization, for a few minutes after the bladder is supposed to have been emptied, a quantity of urine is found in the bladder. The cystoscope usually makes possible only the diagnosis of the condition and gives little information regarding the size of the diverticulum, for it is possible only in rare instances to examine the interior of the diverticulum itself. Regarding the size and the presence or absence of calculus, much can be learned by means of the X-ray. The methods which are usually employed in this study are the curling up of a shadow-graph catheter in the sac, or the filling of the bladder with a solution impermeable to the X-ray, as bismuth, thorium or one of the silver salts as argyrol, collargol or argentide. After filling the bladder with one of these solutions it is examined fluoroscopically and when its outlines are well defined, the plate is exposed with the patient in this position.

Authorities differ in opinion as to the advisability of cystoscoping patients before prostatectomy, some claiming that it is unnecessary and that sufficient information can be gained without this frequently painful procedure. In three cases of this series, two being in my own practice, prostatectomy was advised and the diverticulum overlooked. In one of these cases, the diverticulum was discovered after the bladder had been opened and in the second, it was not until cystoscopy was performed to explain the presence of 16 ounces of residual urine, that the diverticulum was discovered. The third case had had a suprapubic prostatectomy and eight months later a perineal prostatectomy by two different surgeons. Both operations were followed by no improvement, there being 32 ounces of residual urine. The finding of the large diverticulum fully explained the presence of the large residual urine. Both conditions, namely, the enlarged prostate and the diverticulum, should not be attacked at the same time, for in these feeble old men it is better to divide the shock and give them a rest between operations.

In case 7, five diverticula were found, three of them quite large. The three larger ones were resected while the remaining two seemed so small that it was thought unnecessary to do more than dilate the constriction about the neck sufficiently to make them an integral part of the bladder. The patient made an uneventful recovery and at the time of his discharge from the hospital, he had no residual urine. Three months after operation, he returned with 5 ounces of residual urine. A urethral stricture was primarily the cause of the condition and upon investigation, it was discovered that this had contracted causing an increase in size of the two small diverticula. Dilatation of the stricture has caused a disappearance of the residual urine and I hope by this means to render unnecessary an operation for their removal.

TECHNIQUE

As the majority of diverticula are found on the floor of the bladder in the neighborhood of the ureteral orifices, the technique of this removal is frequently difficult. The method of attack which I have usually followed is that suggested by Squier in his Transperitoneal Operation for Bladder Tumor. The sac is first stripped of its covering of peritoneum, and the ureter is located, as transplantation of it may be necessary later. The preliminary introduction of a catheter into the ureter as suggested by Beer, when possible, frequently simplifies the location of the ureter. Now and then the ureter is found emptying into the diverticulum or is firmly attached to the wall of the sac making necessary ureteral transplantation. In carrying out this part of the operation, care must be taken in selecting a point for transplantation which will put the ureter under no tension. Young's idea of carrying the incision into the diverticulum around the ureteral orifice, serves the excellent purpose of preserving the ureteral sphincter, and renders unnecessary the division and transplantation of the ureter.

After the diverticulum has been freed of the peritoneal covering, the bladder is opened above and the diverticular sac packed with gauze, after the method of Cabot and Lower. This procedure greatly facilitated the handling of the diverticulum, and renders less difficult the freeing of external attachments. After it has been completely freed, it is inverted into the bladder cavity, tied off, and divided with a cautery knife. The bladder wall is then reinforced, a stab wound made at the most superior point of the bladder, a Pezzer catheter inserted, and the original cystotomy wound closed. This idea of using a separate opening for the Pezzer catheter was suggested by Squier, and is far superior to its introduction through the upper end of the original opening. The presence of the catheter usually occasions more or less sloughing, frequently resulting in the breaking down of the wound. The suprapubic catheter is removed at the end of a week, and an in-dwelling catheter left in the ureter until the suprapubic wound has healed.

Case 1. D. D. G., age 68, married, admitted July 11, 1910, with the history of frequent urination for three years. Examination revealed an enlarged prostate and on cystoscopy a large vesical calculus was discovered. On July 20, 1910 a flat calculus which measured 2½ inches in diameter was removed through a suprapubic incision. On November 8, 1910 prostatectomy with removal of large adenomatous prostate. Following operation, the cystitis failed to clear up and on August 6, 1910 cystoscopy revealed two calculi. A suprapubic cystostomy was performed. One stone was readily removed but the other of dumb-bell shape was found to be tightly fixed in the neck of a diverticulum, which lay to the left of the midline. Considerable difficulty was encountered in dilating the neck of the diverticulum sufficient to permit of the removal of the stone. This was accomplished, however, and the stone alone removed, as the patient's condition contraindicated further operative procedure. On December 16, 1911, the patient returned to the hospital with profuse hemorrhage per urethram and on the following day the suprapubic wound opened. After continuous irrigation the hemorrhage was controlled. The patient was very weak, remaining in the hospital for three months before the hemorrhage ceased entirely. Surgical treatment was refused and he left the hospital with instruction to irrigate the bladder twice daily. On October

2, 1914, he reports that he was fairly comfortable on bladder irrigations. X-ray revealed diverticulum of left wall of bladder.

Case 2. S., age 80, cotton planter, admitted June 23, 1913, complaining of hematuria with clots and detritus in the urine for three months. On cystoscopy, a diverticulum was found on the base of the bladder to the left of the midline, and blood was seen issuing from the diverticulum. On July 3, 1913, a suprapubic cystostomy was performed and the diverticulum which was small was found to contain a papilloma. The diverticulum was inverted into the bladder, the neck of the sac surrounded by a purse string suture and divided with the cautery knife. Recovery uneventful. The patient consulted Dr. Louis E. Schmidt in 1916 with the history of urinary difficulty and hematuria for several months. Examination showed a very extensive carcinoma almost completely filling the bladder and death followed an emergency cystostomy.

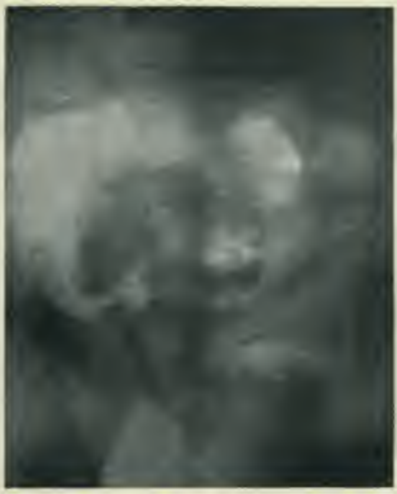

FIG. 1. CYSTOGRAM OF CASE 3

Case 3. Age 60, married, admitted October 23, 1915 with a history of injury to the spine thirty years before, followed by paralysis of the lower extremities. Catheterization was necessary for five weeks, and while he continued to have more or less urinary difficulty, he did not resort to the catheter until ten years later when his physician advised catheterization and bladder irrigation before retiring. He was operated upon one year ago and a vesical calculus removed. Cystoscopy on admission revealed a stone in the bladder. On November 2, 1915, a litholapaxy was performed. Three days later a diverticulum was discovered cystoscopically and on the following day the bladder was filled with argentide and a cystogram taken. At operation on November 16, the bladder wall was found to be $\frac{3}{4}$ inch in thickness. It was impossible to pack the diverticulum and as this portion of the bladder was so densely adherent to the surrounding structures, the diverticulum together with a considerable portion of adjacent bladder wall, was resected. On November 21 paralytic ileus developed and the patient died on November 22.

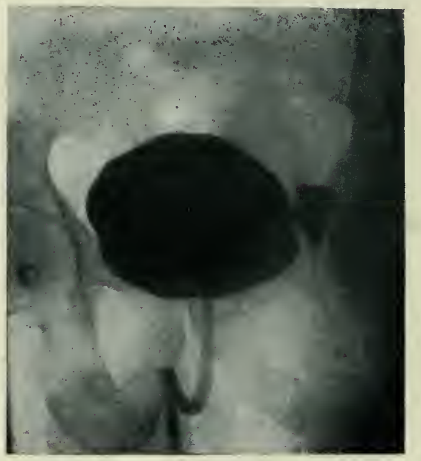

Fig. 2. Cystogram of Case 5 Showing Diverticulum on Left Lateral Wall of Bladder

Case 4. C. Z. K., age 49, widower, admitted December 22, 1913. This patient gave a history of gonorrheal urethritis at the age of twenty, and for the past twenty years has had more or less burning on urination. He passed blood in the urine for the first time six months ago, since which time he has had considerable urinary frequency, which has usually been most marked when walking. The urine was foul and there was a marked cystitis. Bladder capacity 7 ounces. A urethral stricture admitting a No. 20-F. sound was found and cystoscopy showed a diverticulum on the right wall of the bladder. Operation refused.

Case 5. F. F. B., age 32, married. This patient was first seen on April 7, 1915. He gave no history of any previous illness and denied venereal disease. One year before after a strain while lifting he developed a left epididymitis and six months later the right epididymis became swollen. Since this time he has had considerable burning on urination. On examination both epididymes were enlarged. Urine contained long shreds. Blood Wassermann negative. On cystoscopy on April 26, 1916, a diverticulum was found on the left side. Refused operation.

Case 6. F. H. G., age 55, male. Admitted January 23, 1915, with the history of an attack of gonorrhea twenty-five years before. Ten years ago a urethral stricture was found and since this time sounds have been passed at intervals. Three weeks before admission, he began to pass pus and blood and was required to get up four or five times at night. Examination revealed a stricture in the deep urethra, admitting a No. 20-F. sound. This was readily dilated up to No. 28-F., and after silver nitrate irrigations, some improvement was noted. There were 3 ounces of residual urine. The instrumentation was followed by considerable local reaction and on July 23 it was not possible to pass an instrument larger than No. 18-F. This was followed by marked reaction and the patient was admitted to the hospital. On August 13 an internal urethrotomy was performed, following which the condition of the urine improved, although pus was still present. Instrumentation was always followed by chill and elevation of temperature. On November 15, 1915, catheterization revealed 5 ounces of residual urine and urination was accompanied by burning. On December

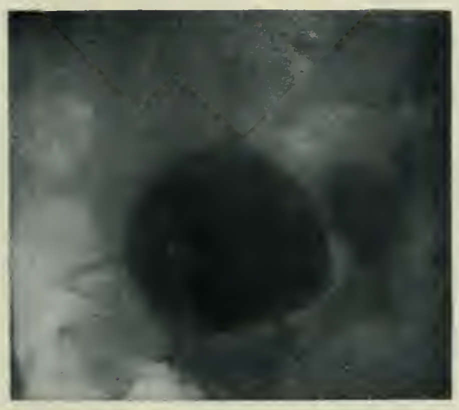

FIG. 3. CYSTOGRAM OF CASE 7

14 the residual urine had increased to 6 ounces and the patient was sent to the Homeopathic Hospital for operation. On January 3, 1915, a suprapubic cystostomy was performed and a large diverticulum resected. Death January 4.

Case 7. C. G., age 42. First seen December 10, 1915, giving a history of four attacks of gonorrhea, the first attack twenty-five years before. Five years ago had urinary frequency and terminal hematuria. On examination the blood and urine were well mixed. A large calibre stricture was found in the posterior urethra and cystoscopy revealed the opening of a diverticulum on the left side. At operation on January 7, 1916, the diverticulum after being packed with gauze was dissected loose from its attachments, inverted and tied off in bladder. Recovery uneventful.

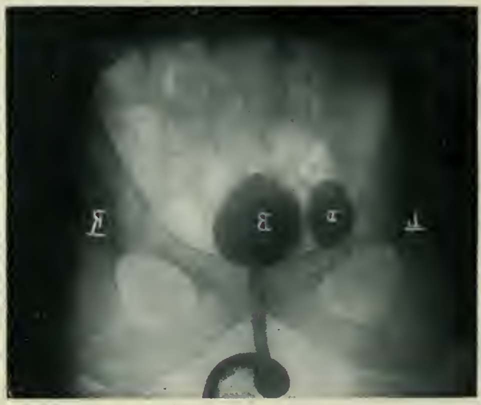

Fig. 4. Cystogram of Case 8 Showing Diverticulum of Left Bladder Wall

Case 8. Dr. J. E. This patient gave a history of scarlet fever seven years before, during which attack he had considerable urinary urgency. Eighteen months ago a small urethral discharge was noted. Shortly after an abscess of the prostate ruptured into the urethra and since this time slight hematuria has been noted at intervals. On October 20, 1916 cystoscopy revealed the orifice of a diverticulum in the region of the left ureter. He was operated upon November 2 and the diverticulum resected. Recovery uneventful.

Case 9. J. D., age 60. First seen on August 24, 1916, giving history of a gonorrheal infection complicated with epididymitis several years before. For twelve years he had noted more or less difficulty in

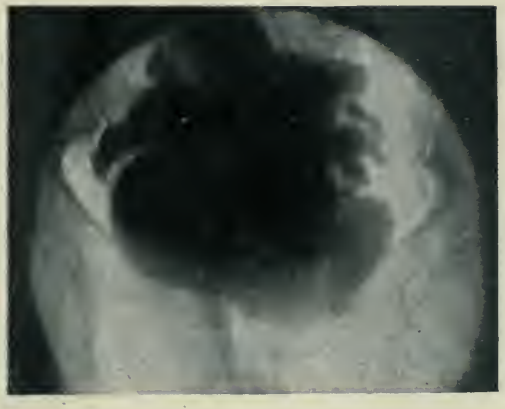

FIG. 5. AFTER THE REMOVAL OF THREE LARGE DIVERTICULA AND THE DIVISION OF THE NECKS OF TWO SMALLER ONES

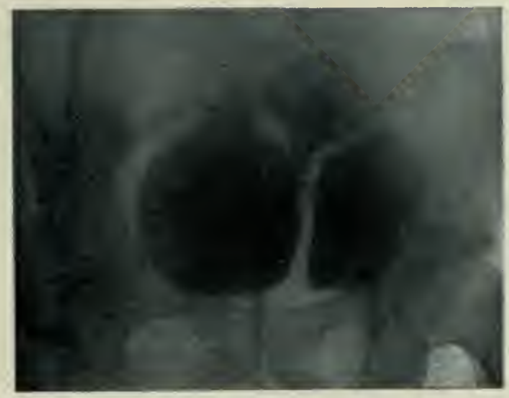

FIG. 6. CYSTOGRAM OF CASE 21 SHOWING TWO LARGE DIVERTICULA ON LEFT LATERAL BLADDER WALL

voiding urine and during the five months prior to his admission, catheterization was necessary. Examination revealed a prostatic median bar, for which condition he was operated September 1, 1916. Following operation, 16 ounces of residual urine were still present and on cystoscopy, three large and two small diverticula were found, this finding being confirmed by the X-ray. On November 13, 1916, the three larger diverticula were removed and the necks of the remaining ones, which were small and very shallow, were dilated until the condition seemed to be corrected. Following this operation, the patient made an excellent recovery. On February 23, 1917, examination revealed 5 ounces of residual urine and at cystoscopy on March 1, the two small diverticula which had been conservatively treated at the former operation had enlarged considerably. Following urethral dilatation the patient was able to completely empty his bladder.

Case 10. S. R. D., age 49. Admitted January 11, 1917, with the history of an attack of gonorrhea at the age of 20. In October, 1915, a suprapubic prostatectomy had been performed, the suprapubic fistula remaining open for eight months. Following some perineal operation, the nature of which could not be learned, the suprapubic wound healed, but the healing of the abdominal wound was followed by the development of a large ventral hernia. From this time on, the patient was unable to empty his bladder and on examination 32 ounces of residual urine were found, together with a stricture in the posterior urethra. The X-ray revealed a large diverticulum at the apex of the bladder. The findings fully account for the large amount of residual urine and explain the inability of the patient to empty his bladder.

Case 11. C. E. B., age 53. First seen March 1, 1917, with the history of hematuria three years ago and more or less pain in voiding for nine or ten years. On examination a stricture of 24-F. calibre was found in the posterior urethra. X-ray revealed two large diverticula on the right wall of the bladder. On March 10 both diverticula were resected. Convalescence uneventful.

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ON THE CONTROL OF THE SYMPTOMS OF DIABETES INSIPIDUS BY SUBCUTANEOUS INJECTIONS OF EXTRACTS OF THE HYPOPHYSIS CEREBRI (PARS POSTERIOR AND PARS INTERMEDIA)

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INTRODUCTION

To be compelled to pass large quantities of urine at short intervals throughout the day and the night and to be forced to drink correspondingly large quantities of water to slake the thirst are symptoms that may become so tormenting as to make the patient manifesting them a real object of compassion. In severe diabetes insipidus the polyuria may, as everyone knows, be extreme; the quantity of urine passed each twenty-four hours often amounts to 10 or 12 litres, in one case on record it was as much as 43 litres. The specific gravity is very low, the kidneys being unable to excrete a concentrated urine. It is hard for a normal person to conceive of the thirst these patients must suffer, if we are to judge of thirst by the amount of water imbibed. The water-intake in Trousseau's famous case reached 50 litres in the twenty-four hours. A patient will sometimes swallow a large pitcherful of water as a single drink and if good drinking water be not available, it is astonishing to what lengths a sufferer may go in the effort to quench his thirst; it has been stated that Strubell's patient, deprived of water, drank his own urine!

In the severe cases of diabetes insipidus, the patients often become very nervous. The pollakiuria and the polydipsia of the day are troublesome enough but at night they interfere with sleep, and few people can experience a prolonged insomnia without growing progressively more disturbed. It is but little wonder then that physicians have sought eagerly for remedies that will mitigate the symptoms of this disease. Many measures have been tried, but, until recently, without success.

It will be clear, however, from the case-history to be recorded here, which is in agreement with a few other case-histories reported between 1913 and now, that we are now in possession of a method of controlling both the urinary output and the thirst in patients suffering from diabetes insipidus, to their great advantage. That method consists in the subcutaneous administration, at certain intervals, of suitable amounts of extracts of the posterior lobe (and pars intermedia) of the hypophysis cerebri. By applying this method, the patient's polyuria and polydipsia can be made to disappear and the kidneys will again excrete a urine of normal concentration.

The history of the patient before the hypophyseal-extract therapy was applied

Katherine L., single, a teacher of music, aged 44, was referred to one of us on February 17, 1917, for special diagnostic study and for treatment, by Dr. Philip S. Roy of Washington, D. C. She complained of passing very large quantities of urine at short intervals throughout the day and the night, of sleeplessness, of nervousness, of excitability, of trembling of the hands and of palpitation of the heart. On admission to the private ward of the Johns Hopkins Hospital a detailed anamnesis was recorded by Dr. F. H. Kruse, of which the following is a summary.

Family History. Negative for diabetes insipidus. Five sisters died in infancy, but, as far as is known, there has been no luetic infection in the family. The father is living and well at the age of 86. The mother died in childbirth at 41. One sister died of pneumonia at 39. Three brothers and two sisters are alive and well.

Previous History. Aside from some severe febrile disease of unknown nature lasting three months when she was eighteen, the patient was healthy until the summer of 1916, when the present illness began. No excess in the use of tea, coffee, or alcohol. Menstruation began rather late (eighteenth year); regular; no dysmenorrhoea; each period lasts about five days; flow rather profuse, more so since last October.

Present Illness. The patient states that her unusual thirst began in September, 1916. She looks upon the thirst as the beginning of her illness, though in the preceding July and August she had felt very tired and listless. When directly questioned she admitted that for at least two years earlier she had felt fatigue more easily than was her wont and had noticed a lack of her accustomed energy. She had, however, gained weight during the summer (increase of 12 pounds between July and October), but she asserts that she gains weight every summer, and loses in winter.

When the thirst began in September, she rapidly increased her fluid-intake, drinking large quantities of water, lemonade, and orangeade. Before long she found that she was drinking from 8 to 10 quarts of fluid in the twenty-four hours. She craved water and sour drinks, but has no especial desire for sweets. She drank about half of the total fluid at night and the amount of urine voided corresponded closely to the amount of fluid ingested. The frequent voiding interfered with her work during the day and kept her from sleeping at night so that she grew ever more nervous and distressed. On one day the urinary output was 11 litres and the specific gravity 1001.

In the middle of October, 1916, she became so weak and nervous that she was compelled to relinquish her teaching. At Dr. Roy's suggestion she remained in bed for a few weeks, during which time she was carefully observed, several important diagnostic tests were made, and a variety of therapeutic measures were tried. Aside from palpitation of the heart and some disturbances of digestion (gaseous eructations; abdominal discomfort), there were no symptoms except those already mentioned. There had been no headache, no flushing, no pains in the limbs, no hemianopsia or other disturbance of vision. The Wassermann reaction was negative in the blood-serum. Nothing abnormal could be made out on ophthalmoscopic examination. The cerebrospinal fluid obtained by lumbar puncture was found to be normal, and the puncture was followed by severe headache. Contrary to J. B. Herrick's experience and that of Dean Lewis, the polyuria in our case remained uninfluenced by the lumbar puncture.

Dr. Roy treated the patient, applying the several drugs that have been advised for diabetes insipidus, but with disappointing results. Codeia, ergot, and bromides had but little if any favorable effect. For some ten days, 1 grain of thyroid-gland substance and 3 grains of suprarenal-gland substance were administered thrice daily without avail. Even pituitrin was tried and abandoned after a few doses. Most benefit seemed to be obtained from the rest in bed; after it, the patient felt stronger and less nervous, but the polyuria, the pollakiuria, the polydipsia, and the insomnia continued.

About the middle of December, Miss L., was permitted to go to the country and to indulge in gentle exercise in the open air. Though she felt weak and nervous and had gaseous eructations, she ate fairly well and continued to drink from 6 to 8 litres of water daily. In February she was referred to us for special study in the hope that, after experiment, some method of controlling the polyuria and polydipsia might be worked out.

Physical examination. On admission to the private ward, general physical examinations were made by several members of the staff (Barker, Sprunt, Carter, Kruse) and a number of tests were made by specialists; the findings may be summarized as follows: Height 5 feet 4 inches; weight 153 pounds; moderate obesity (calculated ideal weight 132 pounds); temperature ranging between 99° and 100° (became normal after five days in the hospital); moderate tachycardia, pulse varying between 90 and 115 (the rate dropped, and after the first week varied between 76 and 83).

Bony framework, medium; acra of head, rather prominent; Roentgenogram of sella turcica, normal; some spacing of the upper incisors; tendency to prognathism; rather marked kyphosis of mid-dorsal spine, but no gibbus; thorax slightly emphysematous in type; pelvis broad.

Skin clear, soft, but rather dry; some pigmentation of the face and especially of the eyelids; hair of head, iron gray, abundant; eyebrows, heavy; long eyelashes; a few hairs on chin and upper lip; hirci and crines abundant and of normal feminine type; subcutaneous fat somewhat excessive, being especially abundant over the back of the neck and in the region of the breasts, though fairly evenly distributed elsewhere; in the extremities, the fat is proximally, not distally distributed; no oedema; tendency to erythema of neck, upper chest, and back.

Muscles well developed; some fine tremor of the fingers; no muscular atrophy. Joints normal. Lymph glands normal.

Pulse accelerated (vide supra); radial arteries just palpable, only slightly thickened; blood pressure on admission 210 systolic, 120 diastolic; it fell gradually until on March 1st it was 175 systolic, 105 diastolic; between March 1 and March 25 the systolic pressure varied between 175 and 185, and the diastolic between 105 and 118. Heart only slightly enlarged; apex beat forcible; aortic second sound loud and ringing; no heart murmurs. No retrosternal dulness. Lungs negative on physical and on roentgenographic examination. Thyroid slightly but definitely enlarged, not pulsating.

Teeth spaced. Infection of the right upper second and third molar roots and of the right lower first bicuspid. Many cervical erosions. Gingival hypertrophy (Dr. C. J. Grieves).[1] Examination of digestive tract otherwise negative. Large mass palpable in abdomen (vide infra).

Urine on admission; pale, day urine 4640 cc., night urine 3650 cc., total 8290 cc. Urine voided almost hourly in amounts ranging from 175 to 560 cc., slightly acid, specific gravity 1001 to 1004; occasionally a faint trace of albumen present; no casts; a few white blood corpuscles seen. Phthalein output, first hour 58 per cent, second hour 10 per cent, total 68 per cent; Ambard's K. = 0.221; urea N in 100 cc. blood = 11 mgm. (For other special studies of the urine in the Chemical Division of the Laboratory of the Medical Clinic, vide infra.)

The kidneys were not palpable. No signs of renal, ureteral, or vesical calculus. External genitals normal. On vaginal examination (Dr. Cullen), cervix uteri small, large myomatous uterus, mass extending upward almost to umbilicus, freely movable.

Blood count: R. B. C. 5,312,000; W. B. C. 13,500; Hb. 76 per cent (Sahli); no parasites.

Wassermann reaction in blood serum negative.

Nervous system: sensation normal; motility normal; deep reflexes markedly exaggerated but equal on the two sides; superficial reflexes normal; coördination normal; psyche, restless and excitable at first when suffering from lack of sleep. Stereoscopic x-ray of skull showed "marked increase of vascularity, especially in the frontal region" (F. H. Baetjer and C. A. Waters.)

Eyes: pupils equal; react to light and accommodation; extraocular movements normal. Slight protrusio bulborum. v. Graefe, Dalrymple and Rosenbach signs positive; Moebius' sign negative. Ophthalmoscopic examination (Dr. Lloyd Whitham):—nearly negative. Possibly slight temporal pallor. Vessels in both eyes somewhat attenuated. Visual fields nearly normal though there is some interlacing of the outlines of the fields for red and green.

Diagnosis. Diabetes insipidus; dyshypophysism; hyperthyroidism; oral sepsis; arteriolar sclerosis with arterial hypertension and arteriolar nephropathy; myoma uteri.

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[1] The infected teeth were extracted and the sockets curetted. The gums were treated.

BRIEF REVIEW OF SOME OF THE NEWER PUBLICATIONS ON DIABETES INSIPIDUS

One has only to consult Futcher's careful review of diabetes insipidus in the second edition of Osler and McCrae's Modern Medicine (1914) to see how many methods of treatment have been tried without success and to learn how unsatisfactory our knowledge of the real nature and pathogenesis of the disorder has been until very recently. The dangers of restricting the fluid intake of the patient are now generally appreciated. Exceedingly interesting observations were made by Tallqvist (1903), E. Meyer (1905–1912) and others, which indicated that the kidneys in diabetes insipidus are incapable of excreting a concentrated urine, and since their studies, some authors have spoken of a "renal type" of the disorder. Careful studies of renal function made by R. Fitz (1914) in Henry Christian's Clinic at the Peter Bent Brigham Hospital in Boston showed that "the kidney as a whole was normal, but gave findings characteristic for vascular hyposthenuria with vessels hypersensitive to chloride stimulation." Fitz concluded that the disease, at least in the case he studied, was "probably not due to a primary lack of ability to concentrate on the part of the kidney." In 1917, J. H. Barach of Pittsburgh reported a case in which the output was 11 litres, but the kidney could concentrate, though only slightly, on increased ingestion of salt and urea.

Two great steps forward were made (1) when the experimental physiologists (E. A. Schäfer and his colleagues Magnus and Herring) began to recognize the effects of a hormone from the hypophysis cerebri upon urinary excretion and (2) when clinicians and pathological anatomists discovered the frequent association of diabetes insipidus with lesions at the base of the brain, especially with lesions (natural or experimental) involving the hypophysis cerebri (E. Frank, 1912; H. Cushing, 1913). The earlier physiological work had indicated that injections of extract of the pars posterior (and pars intermedia) of the hypophysis cerebri caused diuresis in experimental animals. When, therefore, the clinicians and pathologists discovered the frequent association of diabetes insipidus with lesions of the hypophysis cerebri, they put forward the theory, based upon a too uncritical acceptance of the results of the physiologists, that diabetes insipidus is due to a hyperfunction of the posterior (and intermediate) parts of the hypophysis. At times the clinicians were hard put to it to make their observations fit in with this hypothesis, especially when destructive lesions (neoplastic; surgical) were found to be associated with prolonged polyuria, a discrepancy in ideas that did not escape A. Biedl (1913). The known associations, sometimes, of diabetes insipidus with dystrophia adiposogenitalis, the latter known to be due to hypofunction of the hypophysis, should also have shaken faith in the view that diabetes insipidus is due to hyperfunction of the hypophysis. A third important step forward was made by Pentimalli and Quercia in 1912. These investigators found that in the isolated kidney of the rabbit, perfused with Ringer's solution, posterior lobe extract caused constriction of the renal vessels and diminution of the urinary outflow. A fourth step forward, in our opinion a huge stride, was made in 1913 by Farini in Italy, and by von der Velden in Germany. Farini was able to reduce polyuria in two cases of diabetes insipidus and looked upon the disease as due to insufficiency of the hypophysis. The internist, R. von den Velden, working in A. Hoffmann's clinic in Düsseldorf, undertook a revision of the subject of the relation of diuresis in human beings to the injection of hypophyseal extracts. This investigator found that, in human beings with healthy kidneys, the injection of posterior-lobe hypophyseal extracts did not increase but, on the contrary, diminished diuresis.[2] In patients suffering from chronic nephroses, he met with a similar reaction to injections of posterior-lobe extracts; diuresis was never increased; the excretion of both water and NaCl by the kidneys was diminished. While conducting these experiments, a man suffering from diabetes insipidus came, luckily enough, under von den Velden's observation, and he decided to try in this patient the effects of injections of posterior-lobe extracts. He used pituitrin, hypophysin, and pituglandol (the posterior-lobe extracts supplied by different commercial firms) and discovered that all three would compel the kidneys to double or triple the concentration of the urine and to excrete less water in the urine. Indeed, the curves accompanying his article show that on the days when two injections of pituitrin were administered the urinary output became practically normal. Associated with the disappearance of the polyuria the thirst disappeared, the body-weight increased, the patient felt better generally, the feeling of dryness of all the mucous membranes vanished and the appetite improved. The patient had to get up only once or twice at night instead of eight to ten times to urinate. But as soon as the injections were left off, the symptoms reappeared in full severity. Though this author declined at the time to offer an explanation of the mode of action of the pituitrin, and especially stated that "there is little in favor of the idea of a substitution therapy," his clinical-experimental studies were the first to show that substances derived from the posterior (and intermediate) parts of the hypophysis cerebri injected subcutaneously into human beings can make the symptoms of diabetes insipidus disappear as if by magic.

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[2] In the next year (1914), Motzfeldt also found he could check diuresis in a series of fifteen relatively healthy patients by injecting pituglandol whereas anterior-lobe extracts did not exert this effect.

von den Velden's report has been followed by reports from other clinicians, recording similar results in the treatment of diabetes insipidus. We may mention the articles by Farini (1913), Römer (1913, 1914), Biach (1914), Frey and Kumpiess (1914), Umber (1914), Falta (1915), E. Graul (1915), Hoppe-Seyler (1915), Kleeblatt (1915), von Konschegg and Schuster (1915), H. Strauss (1916), K. Motzfeldt (1916), H. Bab (1916), H. Bab (1916–17), and G. Marañon (1917).

At about the time our patient entered the hospital for study, the papers by Bab (1916–17) and by Motzfeldt (1917) came into our hands. In Bab's article, the bibliography is thoroughly and critically sifted; his paper, in our opinion is especially valuable for its careful presentation of the whole subject from the physiological, pathological physiological, and clinical-experimental sides. Bab concludes that the hypophysis cerebri must be regarded as the central regulatory station for the control of the physiological functions of the urogenital system, that diabetes insipidus is the result of a hyposecretion of the pars intermedia (or, sometimes, of a disturbance of the reception of the secretion in the pars posterior, or of the propagation of the secretion in the cerebral lymph-lacunae). He believes that the kidneys, in themselves, are healthy in diabetes insipidus, but that their power to excrete a concentrated urine fails because of the lack of the secretion from the pars intermedia of the hypophysis; the kidneys function normally again if the secretion (from an external source) is supplied through subcutaneous injections. A hyperfunction of the hypophysis cannot be the cause of diabetes insipidus. In Motzfeldt's paper, a series of most interesting experiments carried on in the laboratory of Harvey Cushing's clinic are fully reported. Motzfeldt believes that the discrepancies in the results reported by physiologists are due to the methods employed. In the early experiments (Magnus and Schäfer) anesthetized animals were used and diuresis followed injection of posterior-lobe extracts. In his own experiments Motzfeldt used rabbits, kept quiet, without anesthesia, by placing them upon their backs. Artificial polyuria following the injection of water into the stomachs of these rabbits is definitely checked by subcutaneous injection of posterior-lobe extracts. The effect could be obtained constantly and was proven to be independent of intestinal absorption and of vagal influences. It could be prevented by section of the splanchnics or of the renal nerves near the hilus of the kidney. Motzfeldt concludes that the secretion of the pars intermedia of the hypophysis exerts its anti-diuretic effect through stimulation of the sympathetic nerves, influencing especially the renal vasomotor system.

RESULTS OF THERAPY PERSONALLY OBSERVED

As we have pointed out above, the treatment of diabetes insipidus by various methods, such as restriction of the fluid intake, antiluetic therapy and spinal puncture, has not been consistently successful. It was only when the subcutaneous (or intravenous) injection of the extract of the posterior lobe of the hypophysis was employed that the much sought for relief from this affliction was obtained. Thus far, comparatively few cases treated by this method have been reported and on account of the small number of observations recorded, it would seem essential that the value of hypophyseal extracts in this connection should be substantiated. It might very well be that diabetes insipidus is a syndrome that can be produced not only by insufficiency or other derangement of hypophyseal function but also by other pathological processes. If this should turn out to be true, ultimately instances of the disease would be met with in which the injection of hypophyseal extract would not reduce the increased urinary excretion, and a still clearer conception of the mechanism of what have, until a short time ago, been considered idiopathic polyurias would be arrived at. The treatment of the patient, detailed in this communication, yielded results that did not differ appreciably from those reported by other authors who have injected posterior-lobe extracts. The facts given may, therefore, be considered as confirming previous observations.

Our patient, K. L., was kept throughout her stay in the hospital on a fairly constant diet, low in salt and protein; water was allowed in any quantity desired. In table 1 are given the hourly volume and the salt- and the nitrogen-concentration of the urine before any treatment other than the dietary restriction, mentioned above, was instituted.[3] It will be seen from table 1 that even when the food contained but a small amount of material yielding end-products that are excreted by the kidneys this patient voided a urine, the twenty-four-hour volume of which was above 8000 cc. and in which the hourly quantity rose, at times, as high as 560 cc.; the maximum of salt-concentration was only 0.13 per cent and that of the nitrogen-concentration 0.14 per cent; the specific gravity varied between 1002 and 1004. Further tests performed under similar conditions yielded practically identical results.

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[3] The nitrogen was determined by the Kjeldahl process, and the sodium chlorid according to Volhard, in all the tests.

In carrying out the treatment by subcutaneous injection, two preparations were used: "pituitrin" and "pituitary liquid." Both of these are extracts of the pars posterior (and pars intermedia) of the hypophysis cerebri (or pituitary body), the former being the product of Parke, Davis and Company, the latter of Armour and Company. One preparation apparently is as efficacious as the other. The response of the kidneys to numerous injections was constant throughout, and only a few typical examples are given. The most favorable effect was obtained when two or more injections of not less than 1 cc. each, of either preparation, were given during the course of the day. It may be noted that, in table 2, the second injection was much more potent than the first in reducing the polyuria, in increasing the specific gravity, and in raising the salt- and nitrogen-

TABLE 1

Hourly specimens and analyses of urine uninfluenced by medication

	TIME	URINE					
		Volume	Specific gravity	NaCl		N	
	a.m.	*cc.*		*per cent*	*grams*	*per cent*	*grams*
1	8–9	360	1,002	0.05	0.18	0.07	0.25
2	9–10	245	1,003	0.04	0.10	0.07	0.17
3	10–11	560	1,002	0.05	0.28	0.06	0.34
4	11–12	390	1,003	0.05	0.20	0.07	0.27
	p.m.						
5	12–1	485	1,003	0.05	0.24	0.06	0.29
6	1–2	455	1,003	0.05	0.23	0.07	0.32
7	2–3	280	1,003	0.02	0.06	0.05	0.14
8	3–4	290	1,003	0.02	0.06	0.14	0.41
9	4–5	360	1,003	0.01	0.04	0.08	0.29
10	5–6	280	1,003	0.13	0.36	0.08	0.22
11	6–7	175	1,004	0.04	0.07	0.07	0.12
12	7–8	375	1,003	0.12	0.45	0.08	0.30
13	8–9	385	1,003	0.02	0.08	0.07	0.27
Total day		4,640			2.35		3.39
9 p.m. to 7 a.m.		3,650	1,003	0.05	1.83	0.07	2.56
Total 23 hours		8,290			4.18		5.95

concentration in the urine. From 4 to 8 p.m. the urine of this patient when thus influenced was not very different from that of a normal person. The effect, however, was not a lasting one, since, even in the urine voided a few hours later during the night, there was distinct evidence that the influence of the injected hypophyseal extract was rapidly diminishing. With two injections of 1 cc. each during the day, this patient was made perfectly comfortable, and apparently the efficacy of the extract did not diminish over a period of four weeks' trial in the hospital nor after about one month's continuation of the therapy at home. The patient having once experienced the relief afforded by the injections refused to do without them. On days when other modes of therapy were being tried, she complained bitterly of the symptoms and begged for the injection of the hypophyseal extract.

TABLE 2

Note the marked effect of the second injection of "pituitary liquid" in producing oliguria, in raising the specific gravity, and in increasing the concentration of N *and of* NaCl. *Two injections of 1 cc. of either "pituitrin" of "pituitary liquid" during twenty-four hours constituted the minimal dosage and the smallest number of injections that were efficacious in this patient*

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
8–10 8.30 a.m.*	390	1,005	0.18	0.70	0.13	0.51
10–12	210	1,008	0.24	0.50	0.10	0.21
12– 2	188	1,007	0.14	0.26	0.21	0.39
2– 4 3.45 p.m.*	295	1,005	0.06	0.18	0.15	0.44
4– 6	85	1,013	0.55	0.47	0.41	0.35
6– 8	95	1,010	0.16	0.15	0.43	0.41
Total day..........	1,263			2.26		2.31
Night, 8–8.........	1,430	1,005	0.30	4.29	0.16	2.29
Total 24 hours.....	2,693			6.55		4.60

* 1 cc. "pituitary liquid" intramuscularly.

TABLE 3

The result of a single injection of "pituitary liquid." The effect was only temporary, and did not relieve the patient much

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
9–11 11 a.m.*	515	1,003	0.02	0.10	0.10	0.52
11–1	154	1,010	0.45	0.69	0.19	0.29
1–3	164	1,006	0.15	0.25	0.27	0.44
3–5	112	1,006	0.04	0.04	0.40	0.45
5–7	600	1,003	0.04	0.24	0.11	0.66
7–9	520	1,003	0.02	0.10	0.10	0.52
Total day..........	2,065			1.42		2.88
Night, 9–9..........	5,240	1,003	0.06	3.14	0.07	3.67
Total 24 hours.....	7,305			4.56		6.55

* "Pituitary liquid" 4 cc. intramuscularly.

TABLE 4

Very transient therapeutic results with 0.5 cc. doses of "pituitrin"

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
9–10	540	1,002	0.02	0.11	0.07	0.38
10–11	770	1,002	0.14	1.08	0.04	0.31
11–12	620	1,002	0.02	0.12	0.05	0.31
12–1 12.10 p.m.*	28	1,004	0.19	0.05	0.19	0.05
1–3	120	1,007	0.11	0.13	0.08	0.10
3–5 5 p.m.*	470	1,003	0.21	0.99	0.13	0.61
5–7	90	1,010	0.10	0.09	0.41	0.37
7–9	288	1,005	0.03	0.09	0.22	0.63
Total day..........	2,926			2.66		2.76
Night, 9–9 10 p.m.*	5,160	1,003	0.11	5.68	0.07	3.61
Total 24 hours.....	8,086			8.34		6.37

* "Pituitrin" 0.5 cc. intramuscularly.

The questions now arise: May the quantity of the extract used be diminished, and, may the intervals between injections be prolonged? We must answer, No; not without seriously interfering with the patient's comfort. A single injection, even if it were a large one, was repeatedly found to be inefficient. In table 3, the influence of a single injection of 4 cc. is seen to have lasted but four hours, and did not afford the patient very much relief. Injections of amounts smaller than 1 cc. failed to yield any but very transient therapeutic results (table

TABLE 5

Data from urinary specimens collected in the course of twenty-four hours. "Tethelin" (prepared from the anterior lobe of the hypophysis by Dr. T. Brailsford Robertson) was injected liberally and apparently without effect. A single injection of pituitrin given at 1 a.m. in order that the patient might get some sleep was probably responsible for the slightly increased concentration of salt in the night specimen

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
8 a.m.* 9.00–10.20	610	1,003	0.06	0.37	0.09	0.55
10.20–11.00	680	1,002	0.08	0.54	0.10	0.68
11.00–12.55	595	1,002	0.02	0.12	0.07	0.42
12.55–3.00 1 p.m.*	590	1,003	0.04	0.24	0.10	0.59
3.00–5.00	670	1,003	0.04	0.27	0.07	0.47
5.00–7.00 6 p.m.*	420	1,003	0.04	0.17	0.11	0.46
7.00–8.15	550	1,002	0.02	0.11	0.08	0.44
8.15–9.00	440	1,002	0.01	0.04	0.07	0.31
Total day..........	4,555			1.86		3.92
Night, 9–9 10 p.m.* 1 a.m.†	5,220	1,003	0.17	8.87	0.08	4.18
Total 24 hours.....	9,775			10.73		8.10

* 100 mgm. tethelin subcutaneously.

† Pituitrin, 1 cc. subcutaneously.

TABLE 6

The injection of "adrenalin" did not influence the urinary secretion

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
9.00–10.00	300	1,003	0.04	0.12	0.06	0.18
10.00–11.00	465	1,002	0.04	0.19	0.07	0.33
11.00–11.30*	275	1,003	0.04	0.11	0.04	0.11
11.30–12.30	550	1,002	0.03	0.17	0.05	0.28
12.30– 1.00	290	1,002	0.05	0.15	0.05	0.15

* "Adrenalin" (1: 1000), 10 minims, subcutaneously.

TABLE 7

Urine analyses from specimens collected during a day on which "pituitary tablets" were given by mouth in large doses. The results do not show any improvement over the period when no medicine was given (see table 1).

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
6 a.m.* 9.00–10.00	485	1,003	0.09	0.44	0.06	0.29
10.00–11.00 10 a.m.*	610	1,003	0.03	0.18	0.03	0.18
11.00–11.45	480	1,004	0.06	0.29	0.03	0.14
11.45– 1.00	540	1,004	0.06	0.32	0.05	0.27
1.00– 2.00	435	1,003	0.03	0.13	0.06	0.26
2.00– 3.00 2 p.m.†	515	1,003	0.03	0.15	0.06	0.31
3.00– 4.15	565	1,003	0.02	0.11	0.05	0.28
4.15– 5.00	265	1,004	0.02	0.05	0.07	0.19
5.00– 6.00 6 p.m.†	405	1,003	0.04	0.16	0.06	0.24
6.00– 7.00	440	1,003	0.04	0.18	0.06	0.26
7.00– 7.50	415	1,003	0.04	0.17	0.07	0.29
7.50– 9.00 8 p.m.†	600	1,003	0.03	0.18	0.05	0.30
Total day..........	5,755			2.36		3.01

* Six tablets by mouth.

† Four tablets by mouth.

* NOTE.—Each tablet contained $\frac{1}{10}$ grain extract of the posterior lobe of the pituitary body.

4). On seventeen days injections of "pituitrin" or of "pituitary extract," were given at varying intervals and in different doses and the results carefully observed. The above three examples (tables 2, 3, and 4) represent the practical results that were obtained.

Injections of the anterior lobe of the hypophysis, in the form of "tethelin," kindly supplied by Dr. T. Brailsford Robertson of San Francisco were without effect (table 5). The same was true of injections of "adrenalin" (table 6).

TABLE 8

"Pituitary liquid" (administered by soaking it up in cotton and placing it under the tongue). No changes in the urinary secretion were noticeable

TIME OF DAY	URINE					
	Volume	Specific gravity	NaCl		N	
	cc.		*per cent*	*grams*	*per cent*	*grams*
9–11 9 a.m.*	490	1,003	0.06	0.29	0.10	0.49
11–1	700	1,003	0.04	0.28	0.07	0.49
1–3 1 p.m.*	505	1,003	0.04	0.20	0.11	0.56
3–5	780	1,003	0.02	0.16	0.08	0.62
5–7 5 p.m.*	470	1,003	0.04	0.19	0.11	0.52
7–9 9 p.m.*	760	1,001	0.02	0.15	0.08	0.61
Total day..........	3,705			1.27		3.29
Night, 9–9.........	6,140	1,004	0.09	5.53	0.05	3.07
Total 24 hours.....	9,845			6.80		6.36

* "Pituitary liquid" 1 cc., on cotton, under the tongue.

Administration of the extract of the posterior lobe by mouth in tablet form, even in fairly large doses, did not prove to be of value (table 7). Inasmuch as some drugs are absorbed more readily by the mucous membrane of the tongue and mouth than when they are swallowed, this procedure was resorted to, but without any observable favorable influence (table 8).

Motzfeldt, on the other hand, was able to check the polyuria in his cases by feeding the fresh posterior lobe obtained from the ox. In his experiments on rabbits, he checked diuresis by oral administration but gave relatively enormous doses—fifty times the dose that was efficient on subcutaneous administration.

SUMMARY

The urine of patients suffering from diabetes insipidus may be diminished in amount, its specific gravity can be raised, and the percentage of sodium chlorid and of nitrogen that it contains can be increased by injections of the extract of the pars posterior (and pars intermedia) of the hypophysis cerebri. To afford the patient appreciable relief from the polyuria, it is necessary to administer the "pituitrin" or "pituitary liquid" by subcutaneous injection and to give not less than two doses of at least 1 cc. each in the course of every twenty-four hours. These extracts do not lose their efficiency when given daily over a long period. Administration by mouth was without effect. Tethelin and adrenalin do not seem to be of any value in the treatment of diabetes insipidus.

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A STUDY OF THE EFFECT OF THYROID MEDICATION ON THE BASAL METABOLISM, RENAL FUNCTION AND NITROGEN BALANCE IN CHRONIC NEPHRITIS AND IN HYPOTHYROIDISM

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Peabody, Meyer and Du Bois (1) have found that in patients with compensated cardiac lesions or with mild nephritis the basal metabolism is not increased. Further studies by Aub and Du Bois (2) show that in general the type of nephritis with edema is accompanied by a decrease in the metabolism, and the type of nephritis without edema, by a slight increase in the metabolism. These findings have been confirmed by one of us (Boothby) (3) in his metabolic studies on chronic nephritis.

The possible relation of decreased thyroid activity to low renal function was suggested by Dr. Christian from results obtained from thyroid therapy in the following case.

W. H. C. (Med. no. 426), a male, aged forty-eight years, was admitted to the Medical Service of the Peter Bent Brigham Hospital in October, 1913. This patient had the characteristic appearance and mental attitude of deficient thyroid activity. The symptoms were, however, somewhat masked by a distinct cardio-nephritic element. The urine contained a trace of albumin and was loaded with hyaline and granular casts. The phthalein output was 21 per cent in two hours. He showed some improvement on Karell diet and digitalis for four days. The administration of 0.9 gram thyroid extract for twelve days resulted in still further improvement, both physical and mental. Likewise, the albumin disappeared from the urine and the casts greatly decreased in number. The phthalein excretion in two hours increased to 55 per cent. In December he was discharged much improved. Three months later he was readmitted with marked exacerbation of the cardio-renal symptoms. Thyroid feeding was again tried but without apparent benefit. He passed into coma and died April 2, 1914.

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At autopsy the thyroid was found to be small and markedly atrophic. The kidneys showed a distinct chronic glomerular nephritis and also an acute tubular nephritis. These findings were consistent with the clinical diagnosis of chronic nephritis superimposed on thyroid insufficiency. When the latter element was preponderant, treatment with thyroid extract brought about an improvement in the patient's condition. When the renal disability became more marked, however, no such improvement occurred.

One of us (Boothby) (4) has reported the following case of myxedema with low renal function in which, after thyroid feeding, there was marked improvement both in the degree of hypothyroidism and in the renal function.

M. J. B. (Med. no. 4197), a female, aged sixty-two years, unmarried, entered the Peter Bent Brigham Hospital in February, 1916. The patient had marked edema of the eyelids and moderate edema of the extremities. Her skin was dry, but not especially thickened. There was almost complete loss of hair. The temperature, pulse and respiration were subnormal and she was exceedingly drowsy. The urine was acid, specific gravity 1.015 and a very slight trace of albumin was present. There was no sugar. The sediment contained squamous and white blood cells, occasional red blood cells and a few finely granular casts. Special renal tests showed low kidney function (table 1). The metabolism February 23 was 48 per cent, below normal, indicating marked thyroid insufficiency.

Under intermittent small doses of thyroid (0.07 gram to 0.78 gram) per day, the patient very slowly improved and the metabolism April 29 had increased to 17 per cent below normal. She was beginning, however, to show signs of irritability and consequently the thyroid was discontinued for a time during which the metabolism May 24 fell to 24 per cent below normal.

Thyroid was again administered for ten days during the middle of June. June 27 the final metabolism determination was 17 per cent below normal.

It was impossible to administer thyroid continuously or in sufficient quantities to this patient to bring her metabolism up to normal without producing toxic symptoms. Nevertheless, the physical and mental improvement from thyroid treatment was most marked. The albumin and casts practically disappeared from the urine and there was a slight

TABLE 1

Data of M. J. B. (M. N. 4197).§ Age sixty-two; height 165.4 cm.

DATE	BLOOD UREA NITROGEN IN 100 CC.	INDEX UREA EXCRETION (MCLEAN)	PHTHALEIN (IN TWO HOURS)	METABOLISM FINDINGS											REMARKS
				Weight	Blood pressure	Rectal temperature	Pulse rate	Respiration rate	Ventilation per minute S. T. P. D.	O₂ absorption per minute	Respiratory quotient	Total calories per hour	Calories per square meter per hour	Percentage normal	
1916	*grams*		*per cent*	*kgm.*	*mm.*	*°F.*			*liters*	*cc.*		*Cals.*	*Cals.*	*per cent*	
February 23				56.2	135–95	98.4	66	13	3.17	95	0.94	28.4	17.6	−48*	Very dull, drowsy and lethargic. Marked edema
February 24	18	26	20												
March 10–27															Pleurisy and bronchio pneumonia March 20, 1700 cc. fluid withdrawn from chest. March 27, 530 cc. fluid withdrawn from chest
April 29.....				45.1	115–80	98.6	80	20	7.60	144	0.80	41.4	28.2	−17	Very bright, nervous and irritable. Edema entirely disappeared
May 24.....			26	48.2	115–80	98.8	73	24	5.11	135	0.84	39.3	25.9	−24	Still very bright and not as irritable
June 1......	21	15													
June 27.....				53.8	120–85	97.8	74	20	5.73	154	0.85	44.8	28.2	−17	Brighter and stronger; very little edema. Up and about

§ Diagnosis: Myxoedema; hypertension; chronic nephritis; chronic myocarditis; hydrothorax; hydropneumothorax.

* Thyroid extract administered in grams per day as follows: February 23, 0; February 24 to 29, 0.39 gram to 0.78 gram; February 29 to March 4, 0; March 4 to 10, 0.195 gram; March 10 to 20, 0; March 20 to 31, 0.26 gram; March 31 to April 11, 0; April 11 to 22, 0.065 gram; April 22 to 29, 0; April 29 to 30, 0.065 gram; April 30 to June 11, 0; June 11 to 21, 0.065 gram; June 21 to 27, 0.

increase in the phthalein excretion, from 20 per cent to 26 per cent in two hours. The blood urea nitrogen rose, however, from 18 mgm. to 21 mgm. and McLean's index fell from 26 to 15.

The effect of thyroid medication in three cases of chronic nephritis was reported by Diaballa and von Illyes (5) in 1897. Large doses of thyroid were administered until symptoms of intoxication were produced. There was loss in weight, increase in the urine nitrogen but without diuresis. No improvement occurred in the physical condition of the patients. Percy (6), 1912–13, and Phipps (7) 1916, however, have reported improvement in cases of chronic nephritis after the administration of thyroid.

To determine the effect of thyroid medication on the basal metabolism and renal function detailed studies were made by us of four cases—one of myxedema and three of chronic nephritis. The renal function tests were made by Dr. Bowen[1] and the metabolism studies were carried out by Dr. Boothby.

The first was a marked case of myxedema.

A. A. H. (Med. no. 4976), a female, aged fifty-five years, married, was readmitted to the Peter Bent Brigham Hospital July, 1916. At her previous admission (August, 1914) she presented the typical symptoms of myxedema. The urine was negative. At that time she improved greatly under thyroid medication. At her second admission she showed a moderate degree of myxedema, complicated by low renal function (table 2) and by the presence of albumin and cellular elements in the urine.

During this period of observation the patient was placed on a nephritic diet containing approximately 12 grams nitrogen and 4 grams sodium chloride. The preparation of thyroid used was alpha iodin, a supply of which had been sent us by Dr. Edward C. Kendall (10) of the Mayo Clinic.

The total nitrogen and chlorides eliminated in the urine were determined daily and showed quite wide variations within the space of two or three days, but the average figures for periods of five or six days

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[1] The methods used by us for studying renal function are those in use in the Brigham clinic. For details of the methods see O'Hare, J. P. (8); and McLean, F. C. (9).

TABLE 2

Data of A. A. H. (M. N. 4976).§ Age fifty-five; height 155.2 cm. Diet contained 12 grams nitrogen and 4 grams sodium chloride

DATE	ALPHA IODIN, MILLIGRAMS PER DAY	**AVERAGE NUMBER OF DAYS	FLUID INTAKE (IN 24 HOURS)*	URINE (IN 24 HOURS)*	SPECIFIC GRAVITY*	CHLORIDES IN URINE*	NITROGEN IN URINE*	BLOOD UREA NITROGEN (IN 100 CC.)	INDEX UREA EXCRETION (MCLEAN)	PHTHALEIN (IN TWO HOURS)	METABOLISM FINDINGS											REMARKS
											Weight	Blood pressure	Rectal temperature	Pulse rate	Respiration rate	Ventilation per minute. S.T.P.D.	O₂ absorption per minute	Respiratory quotient	Total calories per hour	Calories per square meter per hour	Percentage normal	
1916	*mgm.*		*cc.*	*cc.*		*gms.*	*gms.*	*mgm.*		*per cent*	*kgm.*	*mm.*	*°F.*			*liters*	*cc.*		*Cals.*	*Cals.*	*per cent*	
								19	26	30												Edematous.
July 16...	0†	5	1,161	1,219	1.012	2.90	5.57	19	24	37	63.2	125–80	98.6	56	20	3.89	136	0.79	39.1	24.0	−31	Slow in speech and action; drowsy; easily confused
July 27...	4	6	1,325	1,171	1.014	1.01	7.60	25	84	57	58.7	115–80	99.2	89	22	6.26	220	0.75	62.7	39.9	+14	Much brighter; speech quickened, less drowsy. Puffiness of face and wrists has disappeared.
August 1..	0	5	1,160	860	1.020	1.01	10.0				56.0	110–80	99.2	84	21	6.21	216	0.77	61.6	40.0	+14	Edema practically gone. Slight thyroid toxemia
August 8..	0	7	1,227	580	1.022	0.24	8.49	29	71		56.6	100–80	98.4	56	14	4.84	152	0.79	43.6	28.1	−20	Not as bright, somewhat drowsy
August 14.	1	6	1,242	863	1.015	0.69	5.87	21	35	30												
August 19.	1	5	1,290	1,193	1.015	1.56	8.04				56.4	110–90	98.8	57	20	5.15	181	0.77	51.7	33.6	− 4	Excellent condition
August 23.	1	5	1,314	862	1.016	1.60	7.59	25	50	35												

§ Diagnosis: Myxedema.

* The figures in the starred * columns represent the average of the determinations of several preceding days, the exact number of which are given in the column with a double star **.

† Alpha iodin administered in milligrams per day as follows: July 16 to 21, 0; July 21, 3 mgm.; July 22, 4 mgm.; July 23 to 26, 6 mgm.; July 26, 9 mgm.; July 27, 4 mgm.; July 28 to August 1, 3 mgm.; August 1 to 9, 0; August 9 to 24, 1 mgm.

are very suggestive. Before the administration of alpha iodin the nitrogen elimination in the urine averaged 5.57 grams and the chlorides 2.90 grams, thus showing slight retention of both nitrogen and chlorides. At the middle of this preliminary period the blood urea nitrogen was in two successive determinations 19 mgm. in 100 cc. and McLean's index was 26 and 24. The phthalein excretion was 30 per cent and 37 per cent in two hours. The basal metabolism was 31 per cent below normal.

All these factors showed a marked change after six days administration of 3 mgm. to 9 mgm. of alpha iodin. The metabolism increased to 14 per cent above normal. The average daily elimination of nitrogen rose to 7.60 grams and there was at the same time an increase to 25 mgm. in the blood urea nitrogen and in McLean's index to 84. The phthalein excretion increased to 57 per cent in two hours. On the other hand, there was a decrease to 1.01 grams in the amount of chlorides eliminated.

Coincident with the increase in the metabolism there was great improvement in the clinical condition. The speech became quicker, the voice higher pitched and the mental attitude brighter. The puffiness of the face and wrists disappeared and there was a distinct decrease in body weight. The temperature was normal but the pulse was slightly elevated.

The dosage of alpha iodin was reduced to 3 mgm. and continued for five days, resulting in a still further increase in the average nitrogen elimination to 10.0 grams while the chloride elimination remained the same. The basal metabolism was still 14 per cent above normal.

As a result of the appearance of toxic symptoms the alpha iodin was discontinued for eight days, resulting in a decrease in the basal metabolism to 20 per cent below normal. The blood urea nitrogen increased slightly to 29 mgm. while McLean's index fell to 71. The nitrogen elimination decreased to 8.49 grams and there was almost complete retention of chlorides. Alpha iodin was again administered in much smaller doses (1 mgm.) and five days later the nitrogen in the urine fell to 5.87 grams and the chlorides rose to 0.69 gram. The blood urea nitrogen fell to 21 mgm., McLean's index to 35 and the phthalein to 30 per cent in two hours. The continuation of thyroid feeding for another five days caused an increase in the basal metabolism to 4 per cent below normal. There was an increase in the nitrogen in the urine to 8.04 grams and of the chlorides to 1.56 grams. Finally, five days later McLean's index increased to 50 with a rise in the blood urea nitrogen to 25 mgm., although the nitrogen in the urine fell to 7.59 grams while the chloride elimination remained the same, 1.60 grams. The phthalein excretion was 35 per cent in two hours.

Throughout there was no fixation of the specific gravity of the urine. It varied quite regularly inversely with the quantity of urine excreted.

In summing up the observations in this case it may be said that the urine nitrogen, the renal activity as determined by McLean's index and phthalein excretion, and the basal metabolism varied directly with the alpha iodin administered. When the proper amount of alpha iodin was given so that the metabolism was maintained at a normal level the patient was in the best clinical condition.

On discharge from the hospital the patient was greatly improved, she was brighter, questions were answered more readily and intelligently, and the rate of expression was quickened.

The other three patients studied were cases of chronic nephritis of varying degree of severity.

H. McP. (Med. no. 4776), a male, aged fifty-eight years, was admitted to the Peter Bent Brigham Hospital June, 1916. The patient had had nephritis for ten years with edema of the legs and abdomen but he had never had any acute symptoms. Save for moderate dyspnea on exertion, there had been no cardiac symptoms. There were albumin and casts in the urine and salt retention but no impairment of nitrogen elimination. Previous to thyroid treatment the patient was on Karell diet, theocin and digitalis but showed no striking improvement. He was then placed on a diet containing approximately 15 grams of nitrogen and 4 grams of sodium chloride. The metabolism was 19 per cent below normal (table 3).

The patient received 0.13 gram of thyroid extract for three days, 0.39 gram for four days, and 0.52 gram for thirteen days, which resulted in a very slight increase in the basal metabolism—June 29 it was 11 per cent below normal and July 10 it was 10 per cent below normal. The patient, however, complained of being "nervous" and there was an increase in the pulse rate; he did not feel as well. The blood urea nitrogen and McLean's index remained constant and the nitrogen salt and fluid balances remained essentially the same. The phthalein excretion rose from 29 to 43 per cent in two hours. The specific gravity of the urine throughout the period of observation was fixed at 1.023.

TABLE 3

Data of H. McP. (M. N. 4776),§ Age fifty-eight; height 185.5 cm. Diet contained 15 grams nitrogen and 4 grams sodium chloride

DATE	THYROID PER DAY	**AVERAGE NUMBER OF DAYS	FLUID INTAKE (IN 24 HOURS)*	URINE (IN 24 HOURS)*	SPECIFIC GRAVITY*	CHLORIDES IN URINE*	NITROGEN IN URINE*	BLOOD UREA NITROGEN (IN 100 CC.)	INDEX UREA EXCRETION (MC LEAN)	PHTHALEIN (IN TWO HOURS)	METABOLISM FINDINGS											REMARKS
											Weight	Blood pressure	Rectal temperature	Pulse rate	Respiration rate	Ventilation per minute. S.T.P.D.	O_2 absorption per minute	Respiratory quotient	Total calories per hour	Calories per square meter per hour	Percentage normal	
1916	*gms.*		*cc.*	*cc.*		*gms.*	*gms.*	*mgm.*		*per cent*	*kgm.*	*mm.*	*°F.*			*liters*	*cc.*		*Cals.*	*Cals.*	*per cent*	
June 23...	0†	1	1,170	1,160	1.017	1.28	11.4	26‡	25‡	29	86.0	145–95	97.8	55	15	6.00	226	0.76	64.4	30.5	−19	Marked edema of legs
June 29...	0.39	5	838	837	1.023	1.94	10.1				83.4	155–100	99.0	70	17	6.55	242	0.76	69.0	33.3	−11	Still edematous; pulse increased
July 5...	0.52	7	983	946	1.023	2.49	12.1	26	29	43												
July 10...	0.52	4	1,483	1,078	1.023	3.01	12.1				82.8	145–95	98.6	73	19	6.22	244	0.79	70.2	33.9	−10	Still edematous; no signs of toxemia, although possible slight tremor of hands
July 14...	0.78	5	983	928	1.023	1.88	11.8															

§ Diagnosis: Chronic nephritis; arteriosclerosis.

* The figures in the starred * columns represent the average of the determinations of several preceding days, the exact number of which are given in the column with a double star **.

† Thyroid administered in grams per day as follows: June 23 to 26, 0.13 gram; June 26 to 30, 0.39 gram; June 30 to July 13, 0.52 gram; July 13 to 15, 0.78 gram.

‡ Determinations made on June 13, 1916.

No demonstrable improvement occurred in this case from the administration of thyroid extract; on the other hand, no obvious ill-effects were produced as occurred in the following case.

J. E. McD. (Med. no. 4855), a male, aged forty-two years, was readmitted to the Peter Bent Brigham Hospital June, 1916. This patient had been under observation in the hospital several times during the past three years. The renal lesion has apparently been progressively increasing as the functional tests at the present time are lower than when he was in the hospital two years ago. He complained chiefly of headache and vomiting and also of dyspnea which was marked on exertion. There was no edema. The urine contained a slight trace of albumin, much granular detritus and rare hyaline casts but no red blood cells.

Before the institution of thyroid feeding the patient was placed on a carbohydrate diet containing approximately 4 grams of nitrogen and 3 grams of sodium chloride, and he was given sweats daily. At this time the basal metabolism was 2 per cent below normal (table 4). A moderate degree of acidosis was present as the tension of CO_2 in the blood was only 29 mm. There was distinct renal insufficiency—the blood urea nitrogen was 79 mgm., McLean's index was 3 and the phthalein was a trace in two hours. The nitrogen elimination in the urine was low—2.67 grams but the positive nitrogen balance was small on account of the low protein diet. There was marked chloride retention.

Thyroid feeding was begun July 6 and a few days later there was a slight decrease in the blood urea nitrogen to 69 mgm. There was at the same time a still further lowering of McLean's index to 0.5 and the phthalein remained a trace in two hours.

Six days of thyroid feeding caused an increase in the elimination of the chlorides to 1.21 grams and of the nitrogen to 3.19 grams. At the end of twelve days of thyroid medication there was a still further increase in the elimination of the chlorides to 1.70 grams and the nitrogen to 4.38 grams. The blood urea nitrogen, however, rose to 86 and McLean's index fell to 0.1 while the phthalein still remained a trace in two hours.

There was still further increase in the elimination of both chlorides and nitrogen at the end of eighteen days of thyroid feeding. But in spite of the negative nitrogen balance the blood urea nitrogen rose to 112 mgm. with some improvement in McLean's index to 1.0. This marked increase in the concentration of urea in the blood was brought about by increased cellular activity as shown by the basal metabolism which was 35 per cent above normal.

TABLE 4

Data of J. E. McD. (M. N. 4855).§ Age forty-two; height 159.0 cm. Diet contained 4 grams nitrogen and 3 grams sodium chloride

DATE	THYROID PER DAY	**AVERAGE NUMBER OF DAYS	URINE (IN 24 HOURS)*	SPECIFIC GRAVITY*	CHLORIDES IN URINE*	NITROGEN IN URINE*	BLOOD UREA NITROGEN (IN 100 CC.)	INDEX UREA EXCRETION (MCLEAN)	PHTHALEIN (IN TWO HOURS)	BLOOD CO_2 VAN SLYKE	METABOLISM FINDINGS											REMARKS
											Weight	Blood pressure	Rectal temperature	Pulse rate	Respiration rate	Ventilation per minute. S. T. P. D.	O_2 absorption per minute	Respiratory quotient	Total calories per hour	Calories per square meter per hour	Percentage normal	
1916	*gms.*		*cc.*		*gms.*	*gms.*	*gms.*		*per cent*	*mm.*	*kgm.*	*mm.*	*°F.*			*liters*	*cc.*		*Cals.*	*Cals.*	*per cent*	
June 20...							79	3	tr	29												
July 5...	0†	1	1,300	1.009	0.89	2.67					51.5	180–135	97.4	54	16	5.77	191	0.92	56.7	37.6	− 2	Very cheerful and good natured. Headaches present and signs of impending uremia
July 11...	0.26	6	2,150	1.010	1.21	3.19	69	0.5	tr													
July 17...	0.52	6	2,000	1.012	1.70	4.38	86	0.1	tr													
July 23...	1.04	6	2,057	1.012	2.53	5.44	112	1		18	50.7	140–110	98.0	88	19	9.46	270	0.84	78.6	52.1	+35	Somewhat drowsy and irritable. Headaches present and uremia seems imminent

July 29...		5	2,560	1.010	2.82	7.46	89	0.8		45‡	49.0	160–115	98.0	79	21	—	251	0.80	72.2	48.8	+27	Thyroid toxemia. Is very irritable and unreasonable
August 3.		6	1,743	1.010	0.70	4.59	70	1		34												Great improvement mentally and physically
August 9.		6	1,780	1.010	0.21	2.32				34	48.8	130–90	98.2	64	16	4.83	178	0.85	52.0	35.1	— 9	Very much brighter; general condition good
August 22							48	2	5													

§ Diagnosis: Chronic nephritis; arteriosclerosis; acute uremia; hypertension.

* The figures in the starred * columns represent the average of the determinations of several preceding days, the exact number of which are given in the column with a double star **.

† Thyroid administered in grams per day as follows: July 5 to 6, 0; July 6 to 12, 0.26 gram; July 12 to 18, 0.52 gram; July 18 to 24, 1.04 gram.

‡ After administration of 80 grams sodium bicarbonate on July 25, 1916.

At this time the CO_2 tension in the blood was only 18 mm. indicating a marked degree of acidosis due to the increase in the non-volatile acid substances in the blood. Eighty grams of sodium bicarbonate were administered and with the neutralization of these excess non-volatile acids the CO_2 tension in the blood was raised to 45 mm. but without producing any clinical improvement in the condition of the patient. In fact, the patient seemed to be on the verge of uremia from imperfect elimination of excess waste products. He was irritable and unreasonable and complained of weakness. There were signs of thyroid toxemia, an increased pulse (from 54 to 79) and tremor of the hands.

Consequently thyroid feeding was discontinued July 24. Five days later the basal metabolism was 27 per cent above normal. The blood urea nitrogen was 89 mgm. and McLean's index was 0.8, but there was an increase in the elimination of chlorides to 2.82 grams and of nitrogen to 7.46 grams. Six days later there was a marked decrease in chloride elimination to 0.70 grams together with a decrease in the nitrogen elimination to 4.59 grams. The blood urea nitrogen was 70 mgm. and McLean's index 1.0. The patient also showed great improvement both mentally and physically,

Seventeen days after thyroid feeding had been discontinued, both chloride and nitrogen elimination were lower than they had been just before thyroid medication was started. The tension of CO_2 in the blood was slightly low—34 mm. The basal metabolism was 9 per cent below normal, showing that the effect of thyroid feeding had entirely disappeared, and that there was possibly a compensatory stage of slightly lowered metabolism due to exhaustion of the cells from recent overactivity Finally August 22, the blood urea nitrogen had fallen to 48 mgm., McLean's index was 2 and the phthalein output 5 per cent in two hours. The patient was very much brighter and his general condition was somewhat better than at the time of entrance into the hospital. Throughout the period of observation the specific gravity of the urine was fixed, only varying between 1.009 and 1.012.

The clinical effect of thyroid feeding in this patient showed that it was probably a dangerous procedure and one that was apt to hasten the onset of a threatened uremia. Likewise, there was no subsequent demonstrable benefit from the use of thyroid that would justify its use as a therapeutic procedure. In the following case it actually appeared to hasten the development of uremia.

F. A. C (Med. no. 4972), a male, aged twenty-four years was admitted to the Peter Bent Brigham Hospital July, 1916. This was a

TABLE 5

Data of F. A. C. (M. N. 4972).§ Age twenty-four; height 175.6 cm. Diet contained 4 grams nitrogen and 3 grams sodium chloride

DATE	ALPHA IODIN. MILLIGRAMS PER DAY.	**AVERAGE NUMBER OF DAYS	FLUID INTAKE (IN 24 HOURS)*	URINE (IN 24 HOURS)*	SPECIFIC GRAVITY*	CHLORIDES IN URINE*	NITROGEN IN URINE*	BLOOD UREA NITROGEN (IN 100 CC.)	INDEX UREA EXCRETION (MC LEAN)	PHTHALEIN (IN TWO HOURS)	BLOOD CO_2 VAN SLYKE	METABOLISM FINDINGS											REMARKS
												Weight	Blood pressure	Rectal temperature	Pulse rate	Respiration rate	Ventilation per minute. S.T.P.D.	O_2 absorption per minute	Respiratory quotient	Total calories per hour	Calories per square meter per hour.	Percentage normal	
1916	*mgm.*		*cc.*	*cc.*		*gms.*	*gms.*	*gms.*		*per cent*	*mm.*	*kgm.*	*mm.*	*°F.*			*liters*	*cc.*		*Cals.*	*Cals.*	*per cent*	
July 16..	0†	2	1,213	1,674	1.015	4.37	10.1	148	1	tr		53.0	125–85	98.0	77	20	9.39	211	0.89	62.2	37.7	−5	Extreme pallor of skin. Hemoglobin 47 per cent
July 22..	4	4	1,108	1,089	1.013	2.28	6.90				21												
July 25..	0	2	725	710	1.017	1.40	4.74	216			15	49.3	125–85	97.6	94	19	9.87	214	0.82	62.0	39.0	−1	Thyroid toxemia
July 30..	0	6	1,392	1,208	1.014	2.06	7.94	214	0.6	0	47‡												Convulsions
August 6	0	6	108	712	1.015	0.62	5.12	223			41												General condition much worse. Patient died on August 12

§ Diagnosis: Chronic nephritis; chronic uremia.

* The figures in the starred * columns represent the average of the determinations of several preceding days, the exact number of which are given in the column with a double star **.

† Alpha iodin administered in milligrams per day as follows: July 16 to 18, 0; July 18 to 21, 3 mgm.; July 22, 4 mgm.

‡ After administration of 120 grams sodium bicarbonate on July 27, 1916.

case of severe nephritis terminating quickly in uremia and death. Previous to the patient's admission the symptoms had been very slight; he complained only of morning dizziness and slight dyspnea.

He was placed on a diet containing approximately 4 grams of nitrogen and 3 grams of sodium chloride. His basal metabolism was 5 per cent below normal but the renal function was low. The blood urea nitrogen was 148 mgm. and McLean's index 1.0. The phthalein excretion was a trace in two hours.

Kendall's alpha iodin was used: 3 mgm. were given for three days and 4 mgm. for one day (table 4). The basal metabolism was 1 per cent below normal. The patient became very weak, vomited frequently, was unable to eat, and in consequence the thyroid was discontinued July 23, five days after it had been started.

Thyroid medication did not appear to influence the nitrogen elimination; there was always a negative balance. The chlorides showed a positive balance when the thyroid was begun and continued to do so after it was discontinued.

Three days after thyroid was stopped the blood urea was 216 mgm. and at the same time acidosis was very marked—the CO_2 tension in the blood had fallen from 21 mm. to 15 mm. After the administration of 120 grams of sodium bicarbonate the CO_2 tension in the blood was increased to 47 mm. There was, however, no improvement in the patient; he was rapidly getting worse. Eight days after thyroid feeding was stopped the blood urea nitrogen was 214 mgm. and McLean's index was 0.6. There was no phthalein excretion at the end of two hours. August 1 acute parotitis with fever and leukocytosis developed. The blood urea increased to 223 mgm. in 100 cc. and the blood CO_2 was still high—41 mm. Death occurred August 12.

In this case the nephritis was severe and it progressed rapidly. Certainly thyroid feeding had no beneficial effect—possibly it may even have hastened uremic coma.

SUMMARY

The effects of thyroid treatment, as measured by clinical, renal function and metabolic studies, are here reported in two cases of myxedema, complicated by symptoms of chronic nephritis, and in three cases of chronic nephritis in which there was no evidence of thyroid insufficiency.

In the first group thyroid medication produced a marked improvement in the clinical and metabolic conditions together with some improvement in the renal function.

In the nephritic cases, however, no improvement occurred from its use, and indeed in two cases decidedly injurious effects were produced.

Thyroid medication, although it has been recommended as a means of satisfactorily treating cases of nephritis, is not indicated unless there is an associated condition of myxedema. The degree of thyroid insufficiency and the effect of treatment thereon can best be gauged by the determination of the basal metabolism.

The authors wish to thank most heartily Miss Russell, Miss Cate, and Miss Sandiford who as laboratory assistants have greatly helped in carrying out the various estimations of renal function and of basal metabolism.

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A COMPARATIVE STUDY OF THE RATE OF EXCRETION OF THE NITROGENOUS WASTE PRODUCTS TO THEIR BLOOD CONCENTRATION IN EXPERIMENTAL URANIUM NEPHRITIS

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It is a well-known fact that consequent to a pathological lesion lowering the permeability of the kidney, there is an accumulation in the blood of the end products of protein metabolism. Furthermore, as the severity of the pathological process advances, the retention takes place in the following order: (1) uric acid, (2) urea and (3) creatinine (1).

In the work presented in this article, we have approached the problem of the order of nitrogenous retention from a new angle. From a comparative study of the rate of excretion to the concentration in the blood for these three nitrogenous end products individually considered (2), we have been led to the conclusion that uric acid normally is eliminated much less readily than either urea or creatinine, and that creatinine appears to be excreted slightly more easily than urea. When, therefore, the permeability of the kidney is lowered, the excretion of uric acid is the first to suffer. In the advanced stages of nephritis, however, the ratio of the concentration of urea in the blood to urea of the urine, may be higher than that for uric acid. Creatinine appears to be the last to show evidences of retention. That such is actually the course of events following failure of renal function is shown by the results of experimental nephritis.

The study of uric acid metabolism has been rendered very difficult by the fact that no animals were available for experimental purposes in which the end product of purine metabolism was uric acid. Moreover in animals the characteristic features of purine metabolism of man are not duplicated. Benedict however has established the fact that the Dalmatian dog, more nearly approaches man in this respect. For this investigation we used two dogs of the Dalmatian breed, which is characterized by black spots and also by its black ears, which hang down. Benedict (3) reports the interesting observation that in twenty-four hours upon a purine-free diet the pure breed of Dalmatian excretes almost as much uric acid as an average adult under similar conditions.

The dogs were kept in clean, dry metabolism cages from which the urine was collected from 9 a.m. to 9 a.m. Toluene was used as a preservative. The blood was drawn from the external saphenous vein, as a rule, after midday. Throughout the experiments the dogs were fed a purine-free diet. Dog 1 took bread, milk and water and dog 2 took only milk and water.

For the determination of uric acid we adopted the Folin, Denis, Benedict method described by Myers and Fine (1) using the water-bath entirely for the evaporation. For the urine, however, we have followed the technique given by Benedict and Hitchcock (4). In estimating the urea of both blood and urine the Van Slyke and Cullen (5) modification of Marshall's procedure was employed. Folin's (6) method was used for creatinine of both blood and urine. The Myers and Bailey (7) modification of the Lewis-Benedict method was adopted for the blood sugar and the method of Benedict (8) for the urine.

The two dogs on which our observations were made eliminated much less uric acid than would be expected of a human being. It would seem therefore that our dogs were not typical of the pure Dalmatian breed. It was noted that in dog 1, the uric acid in the blood gradually diminished after several injections of uranium nitrate. Twenty-five milligrams of uric acid in piperazine (diethylenediamine) solution was injected intravenously. Previous to the injection and one-half hour later, blood was drawn and it was found that the two samples of blood did not differ in their uric acid content. At the same time there was no practical change in the blood urea or creatinine. From this observation we are inclined to believe that the disappearance of the injected uric acid was due to some change of uric acid metabolism. In the case of dog 2, the same phenomena were observed following the injection of uranium nitrate.

By a comparison in the tables for both dogs of the ratios obtained by dividing the milligrams excreted in twenty-four hours by the milligrams in 1 litre of blood, it is evident that after injection the ratio for creatinine is smaller than the ratio for urea. This can be interpreted as establishing the fact that in acute experimental uranium nephritis the creatinine excretion is diminished.

However, after continuing the injections of uranium, the retention of urea becomes very marked, but the creatinine still remains low. In case of dog 1, the urea in 100 cc. of blood reached 388.5 mgm. but the creatinine still remained at 4.6. The ratio between urine and blood for urea and creatinine was 5 and 9 respectively. It seems therefore that creatinine is the last to suffer in kidney insufficiency.

In dog 2, it was noted that the urea of the last specimen of blood reached 277.5 mgm. and the creatinine 4.2. In human cases of acute nephritis of some types it is slighly more difficult for the kidney to eliminate creatinine than urea, also in mild chronic nephritis associated with syphilis and cardiac failure (2). In dog 2 the ratio between the urine and blood for urea and creatinine was 10 and 9 respectively. In this case the dog apparently died in uremia, though at the same time he was afflicted with pneumonia of the right lung. This possibly explains why the blood figure did not rise as high as in dog 1. None the less we may infer from the ratio that creatinine is excreted more readily than urea in severe nephritis or uremic conditions.

Mosenthal (9) has observed that with large doses of uranium the elimination of nitrogen is diminished; but with small doses, the nitrogen excretion may not only remain normal but may even be increased and he believes that this may be due to an increased protein destruction within the body. We have found this to be the case, particularly in dog 2. In this animal the long continued injection of uranium resulted in an increased urea excretion. The increased blood urea under these circumstances would indicate a destruction of protein.

TABLE 1

Dog 1

DATE	URINE						BLOOD				URANIUM INJECTION	CHARACTER OF DIET
	Volume 24 hours	Albumin	Glucose	Urea	Uric acid	Creatinine	Urea per 100 cc.	Uric acid per 100 cc.	Creatinine per 100 cc.	Glucose		
1916	*cc.*		*per cent*	*grams*	*grams*	*grams*	*mgm.*	*mgm.*	*mgm.*	*per cent*	*mgms.*	
July 14	175	–			0.070							Bread and milk
July 15	383	–			0.076							Bread and milk
July 16	357	–			0.046							Bread and milk
July 17	315	–			0.127							Bread and milk
July 18	363	–			0.064							Bread and milk
July 19	170	–			0.058							Bread and milk
July 20	505	–			0.042		26.0	0.69	1.5	0.12	7	Bread and milk
July 21	398	+			0.061							Bread and milk
July 22	340	++			0.057							Bread and milk
July 23	740	++			0.023							Bread and milk
July 24	510	+++			0.027		34.5	1.33	1.9	0.12	3	Bread and milk
July 25	593	+++			0.015							Bread and milk
July 26	747	+++			0.017							Bread and milk
July 27	582	+++			0.024		49.5	0.75	1.7	0.09	5	Bread and milk
July 28	1,052	++			0.026							Water
July 29	757	++			0.015							Water
July 30	1,444	++	0.50		0.011							Water
July 31	1,033	+			0.015		37.5	2.10	1.7	0.11	5	Water
August 1	1,490	+			0.016							Water
August 2	1,064	+			0.014							Water
August 3	1,060	+			0.015							Water
August 4	1,070	+			0.045		42.0	0.72	2.5	0.13		Water
August 5							52.5	Trace	...	....		Water

August 14.........	635	+	0.50	29.3	0.105	0.556						Heavy meat diet
August 15.........	460	–	0.50	13.8	0.026	0.155	82.5	Trace	1.8	0.13		Milk, bread, water
August 16.........	175	–	0.33	5.6	0.027	0.146						Milk, bread, water
August 17.........	115	–	0.20	1.4	0.005	0.153	15.0	Trace	1.5	0.11		Milk, bread, water
August 18.........	265	–	0.30	3.0	0.012	0.098						Milk, bread, water
August 19.........												Milk, bread, water
August 20.........												Milk, bread, water
August 21.........	280	–	0.27	3.2	0.019	0.154						Milk, bread, water
August 22.........	330	–	0.29	4.2	0.017	0.172	19.5	Trace	1.5	0.12		Milk, bread, water
August 23.........	340	–	0.30	4.1	0.018	0.181						Milk, bread, water
August 24.........	537	–	0.23	3.5	0.014	0.171						Milk, bread, water
August 25.........	330	–	0.28	2.5	0.007	0.120					10	Milk, bread, water
August 26.........	615			5.2	0.024	0.249						Milk, bread, water
August 27.........	440			2.5	0.006	0.117						Milk, bread, water
August 28.........	788	+	0.49	4.6	0.010	0.172	21.0		1.0	0.10	10	Milk, bread, water
August 29.........	306	++	0.56	3.7	0.009	0.121						Milk, bread, water
August 30.........	791	++	0.43	5.5	0.011	0.188						Milk, bread, water
August 31.........	590	++	0.56	5.2	0.010	0.174	27.0		1.0	0.11	25	Milk, bread, water
September 1.....												Milk, bread, water
September 2.....	403	++	0.83	3.7	0.016	0.174						Milk, bread, water
September 3.....	510	++	0.91	4.4	0.012	0.179					30	Milk, bread, water
September 4.....	583	+++	0.95	4.1	0.011	0.158						Milk, bread, water
September 5.....	585	+++	1.00	3.6	0.004	0.163						Milk, bread, water
September 6.....	780	++	1.00	4.4	0.005	0.150	30.0		1.4	0.13	50	Milk, bread, water
September 7.....	653	++	1.00	4.2	Trace	0.149						Milk, bread, water
September 8.....	802	++	0.83	3.4	Trace	0.141					100	Milk, bread, water
September 9.....	1,285	++	0.59	4.4	Trace	0.165						Milk, bread, water
September 10.....	1,260	++	0.54	4.3	Zero	0.146						Milk, bread, water
September 11.....	1,730	++	0.42	4.9	Zero	0.171					200	Milk, bread, water
September 12.....	1,675	++	0.36	4.0	Zero	0.147						Milk, bread, water
September 13.....	1,630	+	0.37	5.9	Zero	0.165						Milk, bread, water

TABLE 1—Continued

DATE	URINE						BLOOD				URANIUM INJECTION	CHARACTER OF DIET
	Volume 24 hours	Albumin	Glucose	Urea	Uric acid	Creatinine	Urea per 100 cc.	Uric acid per 100 cc.	Creatinine per 100 cc.	Glucose		
1916	*cc.*		*per cent*	*grams*	*grams*	*grams*	*mgm.*	*mgm.*	*mgm.*	*per cent*	*mgm.*	
September 14*.....	1,457	+	0.33	13.1	0.300	0.813						Water only
September 15.....	1,075	+	0.38	4.4	Zero	0.109						Water only
September 16.....	835	+	0.32	4.6	Trace	0.094						Water only
September 17.....	538	+	0.33	3.6	Trace	0.087						Very little water
September 18.....	395	+	0.26	3.1	Zero	0.055						Very little water
September 19.....	220	+	0.24	2.2	Zero	0.042	388.5	0.50	4.6	0.31		Very little water
						Dog 2						
December 21......												About 900 cc. milk
December 22......												About 900 cc. milk
December 23......	240	–	–	2.2	0.016	0.080						About 900 cc. milk
December 24......	245	–	–	1.7	0.014	0.073						About 900 cc. milk
December 25......	360	–	–	2.6	0.023	0.091						About 900 cc. milk
December 26......	345	–	–	2.6	0.015	0.093						About 900 cc. milk
December 27......	655	–	–	2.8	0.020	0.108	24.0	3.9	1.3	0.12		About 900 cc. milk
December 28......	510	–	–	3.8	0.020	0.059					5	About 900 cc. milk
December 29......	530	–	0.30	2.7	0.021	0.110						About 900 cc. milk
December 30......	560	+	0.33	3.9	0.020	0.122						About 900 cc. milk
December 31......	550	+	0.33	4.4	0.026	0.129						About 900 cc. milk
1917												
January 1........	600	+	0.50	4.1	0.011	0.157	33.0	3.3	1.2	0.16	5	About 900 cc. milk
January 2........	500	++	0.56	3.0	0.011	0.104						About 900 cc. milk
January 3........	510	++	0.53	2.8	0.008	0.103						About 900 cc. milk
January 4........	510	++	0.51	2.7	0.009	0.096						About 900 cc. milk

January 5........	570	++	0.57	3.3	0.006	0.105						About 900 cc. milk
January 6........	520	++	0.59	3.2	0.006	0.083	27.0	2.9	1.7	0.12	10	About 900 cc. milk
January 7........	495	++	0.67	4.5	0.010	0.051						About 900 cc. milk
January 8........	620	++	0.67	4.1	0.011	0.123						About 900 cc. milk
January 9........	485	+	0.50	3.6	0.018	0.087					20	About 900 cc. milk
January 10........	600	++	0.40	3.4	0.009	0.093						About 900 cc. milk
January 11........	540	++	0.45	3.9	0.008	0.110						About 900 cc. milk
January 12........	640	++	0.31	3.6	Trace	0.074					40	About 900 cc. milk
January 13........	370	++	0.31	2.8	0.004	0.054	45.0		2.0	0.11		About 900 cc. milk
January 14........	615	++	0.40	4.6	0.013	0.166					60	About 900 cc. milk
January 15........	460	++	0.63	3.5	0.009	0.093						About 900 cc. milk
January 16........	560	+++	0.44	4.4	0.016	0.118						About 900 cc. milk
January 17........	515	+++	0.42	4.4	0.007	0.119						About 900 cc. milk
January 18........	582	+++	0.63	3.7	0.005	0.086					110	About 900 cc. milk
January 19........	590	++	0.50	6.5	Trace	0.187						About 900 cc. milk
January 20........	515	++	0.55	5.4	0.006	0.128					200	About 900 cc. milk
January 21........	600	++	0.45	5.2	0.011	0.187						About 900 cc. milk
January 22........	547	++	0.33	3.3	0.004	0.068					300	About 900 cc. milk
January 23........	585	++	0.45	4.4	0.006	0.128						About 900 cc. milk
January 24........	530	++	0.42	4.7	0.004	0.089					400	About 900 cc. milk
January 25........	595	++	0.40	4.4	Trace	0.123						About 900 cc. milk
January 26........	600	++	0.37	4.2	0.004	0.081						About 900 cc. milk
January 27........	460	++	0.37	3.8	0.008	0.117					500	Milk + H_2O 400 cc.
January 28........	620	++	0.43	5.3	0.011	0.122						Milk + H_2O 400 cc.
January 29........	530	++	0.43	5.2	0.015	0.106						Milk + H_2O 400 cc.
January 30........	675	++	0.30	4.6	0.013	0.090						H_2O 700 cc.
January 31........	660	++	0.27	4.5	0.009	0.076						H_2O 700 cc.
February 1........	575	++	0.29	4.7	0.008	0.077						H_2O 700 cc.
February 2........	252	++	0.26	2.7	0.006	0.039	277.5	1.9	4.2	0.13		H_2O 400 cc.

* On this day operation was performed to take blood from the external saphenous vein.
Bodyweight 6 kilo for both dogs.

The retention of urea and creatinine appeared gradually in dog 1, after the injection of uranium nitrate, the retention of creatinine, however, being less than that of urea. The experiments of table 1 were discontinued from August 5 to August 14. But this lapse of time was not sufficient for the nephritis to clear up. Three days later, the urea in the blood suddenly came down, and the albuminuria ceased. Injections were resumed on August 25. In this series of experiments likewise, it was noted that the urea retention was more marked than creatinine. In these experiments the observations previously made on dog 2, were confirmed.

TABLE 2

Relationship between the rate of excretion and the concentration of the blood. Milligram excreted per twenty-four hour divided by milligram per 1000 cc. blood.

DOG 1			DOG 2		
Date	Urea	Creatinine	Date	Urea	Creatinine
1916			1916		
August 15	167	86	December 27	114	80
August 17	94	102	1917		
August 22	221	114	January 1	125	132
August 28	219	172	January 6	116	49
August 31	192	174	January 13	61	26
September 6	146	107	February 2	10	9
September 20	5	9			

Dr. J. Oliver at the Rockefeller Institute has kindly examined the kidney sections. He has reported that the kidney of dog 2 shows healthy epithelium in the proximal convoluted tubules. The pathological report harmonizes with the chemical findings. In dog 2, the excretion of urea was greater than in dog 1. It will be recalled that the greater part of the urea is secreted through the proximal convoluted tubular epithelium (10), and that the regenerated epithelium as seen in dog 1 has not the power of secreting urea (11).

Pathological reports

Dog 1. The process is much more severe in this kidney than in dog 2. The cortex contains practically no normal proximal convoluted tubules, but is filled with cystic spaces lined with irregular regenerated epithelium, formed by the dilatation of these structures. The same marked dilatation of the tubule is seen in the outer zone of the medulla and there is also the usual proliferation of the connective tissue. Many casts in the collecting tubules and numerous red blood cells are present in the dilated tubules in the cortex, though no very definite hemorrhages are seen in the glomeruli. The liver is normal.

Dog 2. The sections of kidney show a severe chronic nephritis of the typical uranium type. The glomeruli show in some cases a moderate fibrous thickening of connective tissue around the capsule. The upper part of the proximal convoluted tubule is, however, still fairly well preserved, in many places entirely normal, in others dilated. The lower portions of the proximal convoluted tubule, lying in the lower layer of the cortex and in the outer stripe of the outer zone of the medulla, are severely affected. The normal epithelium is replaced by an irregular epithelium. Many tubules are collapsed by the proliferating connective tissue, others show a marked dilatation. There are a few necrotic cells, but very little evidence of recent acute damage. There are many casts, mostly hyaline, in the collecting tubules. The liver is normal. A section of lung shows the alveolar spaces filled with exudate and polymorphonuclear leucocytes.

SUMMARY

A comparative study of the ratio of the rate of excretion to concentration in the blood for the nitrogenous waste products, shows that in experimental uranium nephritis creatinine is eliminated with slightly greater difficulty than urea in mild cases of nephritis; whereas in the severer types, the urea retention is more marked than that of creatinine. After several injections of uranium nitrate, the uric acid metabolism appears to be altered.

The author is indebted to Prof. V. C. Myers and Asst. Prof. M. S. Fine, for the opportunity to study this problem.

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A NEW UNIVERSAL URETHROSCOPE

WITH NEW DIAGNOSTIC AND THERAPEUTIC FIELDS OF APPLICATION

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Although a large number of urethroscopes have been devised, for each of which claims of superiority over all others are put forth by their various inventors, it has seemed to me, in the course of studies on diseases of the urethra, that one fruitful field for the exercise of therapeutic endeavors through a modern urethroscope had been overlooked, namely, the treatment of filiform strictures of the urethra. It was for the purpose of visualizing the orifice of filiform strictures and for the introduction of filiform bougies under the control of the eye, that a new and useful urethroscope was devised. This was finally developed into a sort of universal cysto-urethroscope, an instrument with a wide field of utility. Recent experience has suggested, that, if the same instrument were modified, it would incorporate the functions of more than one type of urethro-vesical endoscope, serving with slight interchange and re-assemblage of parts, either as,

(1) A straight endoscope for the anterior urethra.

(2) An aero- or air inflation urethroscope.

(3) An operating and catheterizing non-prismatic direct cystoscope.

(4) An irrigating or water dilating non-prismatic telescopic urethroscope.

(5) A special operating telescopic urethroscope.

(6) An Elsner-Braasch cystoscope.

(7) A Kelly or Luys endoscope and cystoscope.

In short, it embodies in its construction features of the simple endoscope, the Goldschmidt, Brown and Geiringer instruments, modified in such a way, as to give it a wide sphere of utility.

Description of the instrument. The urethroscope consists of a straight endoscopic tube (fig. 1), two obturators, a light carrier (fig. 2), a telescope (fig. 3), and a magnifying window (fig. 4 *a*).

The straight tube is longer than that of the ordinary urethroscope ($7\frac{1}{4}$ inches) so as to be available for work in the bladder as well as in the urethra. Near the ocular end (fig. 5 *a*), a large catheter outlet, of the type used in the author's operating cystoscope, is fused into the tube. Through this, special operating devices, such as rongeur forceps, fulguration electrode, filiform and larger bougies, catheters, and applicators may be passed. And, since the direction of this outlet, and, therefore, the exit of entering devices is downward, the operator can manipulate more satisfactorily through it than through a straight endoscopic tube, vision being undisturbed by an intervening hand or instrument.

The endoscopic tube is reinforced at the ocular end by a flange, and admits the light carrier (fig. 2) with a water tight joint.

Two faucets also fit into the cuff. These give entry and exit to fluid for the distention of the urethra, making for an improvement in the clarity of the visual field, and for better manipulation of the instrument.

Two sizes of endoscopic tubes are provided, no. 24 and 25 French, these having been found most useful, it being optional with the surgeon as to which instrument he will select for routine work.

The obturators are designed either for work in the anterior urethra or in the posterior urethra and bladder. An obturator with a short blunt conical extremity serves for work in the anterior urethra. The short obturator must be chosen for the cases in which we desire to treat filiform strictures of the urethra, lesions in the anterior urethra, or where we wish to remove foreign bodies from the anterior or bulbo-membranous urethra. The curved, beaked obturator is to be selected whenever the instrument is to be inserted into the bladder.

The light carrier (fig. 2) differs materially in its construction from any other previously designed, in that it is composed of a sector of a thin tube that fits tightly against the inner wall of the endoscopic sheath, and bears the irrigating tubule. It is equipped with a delicate lamp, which extends beyond the carrier, being of such length that its rays can emerge and illuminate the usual endoscopic field. This type of light carrier possesses advantages over the usual forms, particularly in that its rigidity tends to maintain it in close apposition with the sheath.

At the proximal end of the light carrier is the cuff (fig. 2*a*) for the attachment of the electric contact (fig. 2*b*) and its joint for the introduction of either the telescope (fig. 3) or the magnifying window (fig. 4*a*).

Occupying one of the furrows at the side of the lamp tube, is a fine tube, or tubule (fig. 2*d*) that has its inlet at the faucet (fig. 2*e*) and allows the irrigating fluid to escape at the objective end of the apparatus. Only in this way, is it possible to obtain adequate cleansing of the urethral field when the instrument lies beyond the internal sphincter. When the urethroscope enters the bladder, irrigation may be effected without recourse to this irrigating tubule. The normal flow of fluid with the instrument in the urethra then, is a current that begins at the far, or objective, end of the instrument and flows back and out through the second faucet at the ocular or proximal end.

The telescope. This is of the direct, non-prismatic, forward vision type, and its lens system so designed that a sufficiently wide visual angle offers a view of operating instruments soon after they emerge from the sheath. It is held in a truncated conical fitting that locks into the cuff receptacle of the light carrier tube. However, it is not rigidly held except when the washer screw is tightly secured (fig. 3*c*), a forward and backward movement being permitted when the screw is loosened. This retrograde movement of the telescope is provided for the contingency which arises when operative devices are thrust through the sheath and a better view of their working end is desired. It will be found that a considerable portion of an operative instrument must needs be exposed beyond the sheath for a good view. If we pull back the telescope, however, we may work the jaws of the operating device at a short distance from the tube, sacrificing merely a small portion of the field thereby, but in no way impairing the utility of the visual instrument.

The magnifying window. In order to convert the telescopic instrument into an air inflating instrument, or an Elsner-Braasch cystoscope (fig. 4), or into an ordinary straight tube urethroscope, a magnifying window is provided, which serves, not only to close the tube for air inflation or water distension, but also magnifies the direct picture slightly, and obviates the necessity for accommodation of the eye at so close a distance. Thus, if we withdraw the telescope and attach the magnifying window, we may see the ureters according to the Elsner method, and examine the urethra by the same method, or, we may mop out the sheath, aspirate the contents of the urethra through the tubule Fig. 2 *d* and inspect or treat according to either the air inflation or simple open air method.

In short, the instrument is *universal* in that it combines the uses of the following:

(1) An open air anterior urethroscope and posterior urethroscope.
(2) An air inflation anterior and posterior urethroscope.
(3) A direct telescopic cystoscope (to replace the Brown).
(4) A direct telescopic operating cystoscope.
(5) An operating, irrigating anterior and posterior non-prismatic telescopic urethroscope.
(6) An Elsner-Braasch urethroscope and cystoscope.
(7) A Kelly or Luy's endoscope and cystoscope.

Technic with the irrigating instrument. This universal cysto-urethroscope is chiefly recommended as an irrigating telescopic instrument for the neck of the bladder, posterior and anterior urethra. The technic of its use is as follows.

The sheath fitted with the curved obturator is introduced into the bladder (fig. 1), the obturator removed, and the bladder irrigated if necessary. The light carrier (fig. 2) and telescope (fig. 3) are now locked in place (fig. 5 and the irrigating fluid allowed to flow through one of the faucets a rubber tip or cap having been adjusted at (fig. 5 *a*) the catheter outlet. The trigone, ureters, *bas-fond,* and the posterior wall of the bladder may be adequately illuminated and brought into view, and we may then proceed with the examination of the neck of the bladder and urethra.

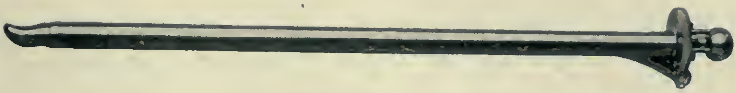

Fig. 1. The Sheath or Endoscopic Tube with Beaked or Curved Obturator in Situ

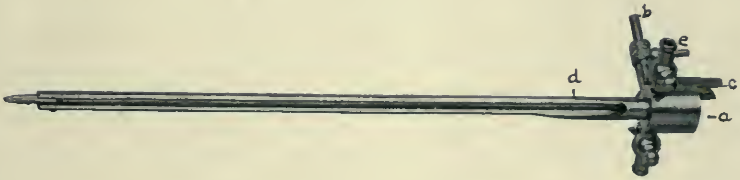

Fig. 2. The Light-Carrier

a, Cuff, carrying two faucets; *b,* electric coupling; *c,* locking fork; *d,* irrigating tubule; *e,* faucet for inflow.

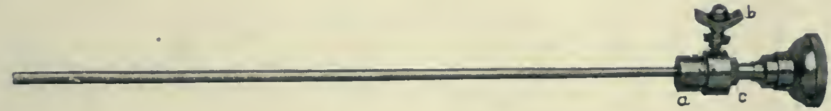

Fig. 3. Telescope

a, Conical fitting; *b,* locking screw fitting into figure 2 *c*, *c,* washer screw.

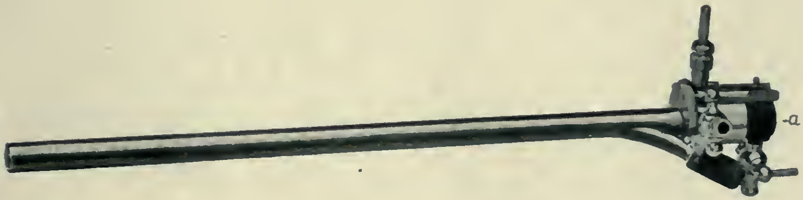

Fig. 4. Sheath or Endoscopic Tube with Light-Carrier

a, Magnifying window, making assemblage for air inflation, ordinary single endoscopy or Elsner-Braasch cystoscopy.

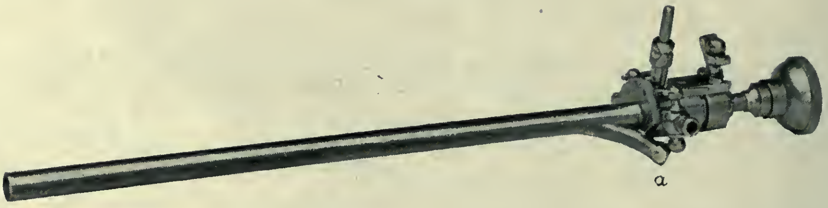

Fig. 5. Complete Assemblage: Sheath, Light Carrier and Telescope
a, Large catheter outlet to which suitable rubber cap or tip must be attached.

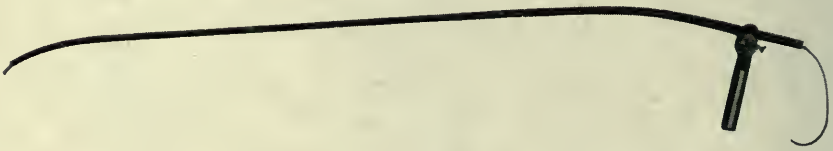

Fig. 6. Author's Special Fulgurating Electrode

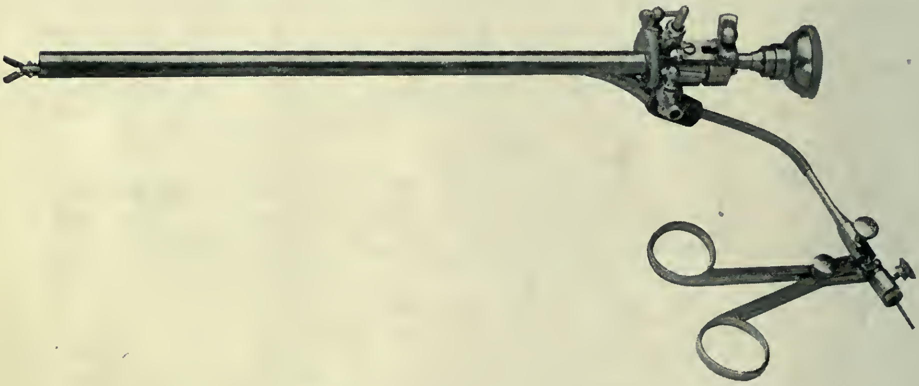

Fig. 7. Universal Urethroscope with Grasping Forceps Inserted

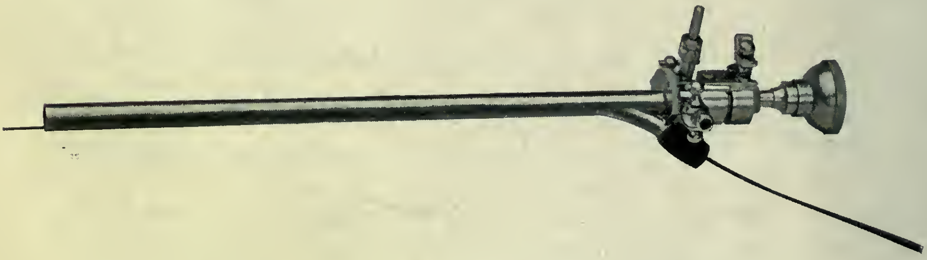

Fig. 8. Complete Assemblage with Philips Filiform Bougie in Place

For those who employ the direct cystoscopic method by preference, both ureters may be catheterized according to the well-known principles of manipulating non-prismatic cystoscopes.

When the neck of the bladder and urethra are to be examined with the water flowing, the instrument is slowly withdrawn a periscopic view of the urethra being obtained, the supra-montane, membranous montane, bulbous and anterior urethra successively appearing. As soon as the membranous urethra is brought into view, it is well to grasp the penis with the left hand, whilst the right hand manipulates the cysto-urethroscope, in order to prevent reflux of the irrigating fluid, the amount of dilation of the urethra being controlled both by the height of the irrigator, and the patency of the irrigating faucet.

As a catheterizing cystoscope. Although the universal urethroscope is not primarily intended for ureteral catheterization, it may be occasionally used for this purpose, and two no. 6 French catheters may be introduced during the course of other work with this instrument, should the necessity of obtaining specimens from the ureters arise. The technic is the same as that with the direct non-prismatic type of cystoscope (Brown), and the instrument may, therefore, appeal to those who are in the habit of employing the direct method of catheterization. After specimens have been obtained, the catheters may be withdrawn, a closed rubber tip attached to the catheter outlet, and the instrument may then be used as a urethroscope.

For those who are in the habit of employing the Kelly or Luys methods, this instrument may be converted into a Kelly or Luys endoscope; or, into an irrigating cystoscope of the direct non-prismatic type. By removing the telescope and inserting the magnifying window (fig. 4*a*), the universal urethroscope may at once serve as an Elsner-Braasch cystoscope, possessing distinct advantages over the latter in that it will permit of the introduction of one large catheter, and of operating devices.

As an operating cystoscope. Although the instrument will not supersede the author's operating cystoscope for special operative work in the bladder, it may be preferred as an operating cystoscope by those who are experienced in the Kelly and

Elsner-Braasch methods, since the technic of its application will be found easy to master by such workers. With the instrument introduced in the usual fashion and the bladder washed out, observation cystoscopy is first carried out, a foreign body is viewed, or a ureter put into the field, or a tumor or ulcer inspected, as the case may be.

To fulgurate, a properly selected tip is adjusted to the catheter outlet and the special applicator or wire introduced just as in the author's operating cystoscope, it being remembered that the absence of a catheter deflector necessitates working at close range to obtain a precise application of the electrode against the tumor. For fulguration at the neck of the bladder, for lesions at the sphincter, and for tumors that have their origin at the urethra side of the sphincter, a most satisfactory view is obtained and the mechanical factors for successful employment are almost ideal. For fulguration in the trigonal, sphincteric, and juxtasphincteric regions, the author's special hard rubber curved electrode (fig. 6) is recommended. For dilatation of the ureters the instrument possesses some advantages over the indirect type of cystoscope, because it can be brought more directly in line with the ureteral orifice. Catheters of increasing size, bougies, a special type of Philip's filiform (Buerger) (Fig. 8), or Buerger's olivary dilators may be employed.

For removing foreign bodies (fig. 7) such as small ureteral calculi that have decended into the bladder, the urethroscope may be occasionally useful. The foreign body is held, pushed beyond the field of vision, the instrument as a whole removed, the foreign body in the grasp of the forceps following in the manner suggested by the author when the operating cystoscope is employed.

For snaring papillomata a small sized snare will be found serviceable, although the lack of the deflector makes the snare more difficult to manipulate than through operating cystoscope.

For intravesical biopsy the urethroscope will be valuable particularly when the specimens are to be removed from the region of the neck of the bladder.

As a posterior urethroscope. In routine examinations the author's cysto-urethroscope possesses distinct advantages over the universal, in that it is not so likely to cause traumatism. Furthermore, the Buerger cysto-urethroscope may be moved backward and forward and pushed inward and outward frequently during the examination, without incurring the risk of producing hemorrhage, making a more thorough examination possible, even in difficult cases in which the *universal cysto-urethroscope* would be less satisfactory. However, the value of the universal urethroscope, i.e., the direct telescopic type of vision in the urethra, should not be underestimated, there being a distinct field of application for this method of examination.

The urethral view is different from that obtained with the prismatic telescope, a sort of periscopic picture of panoramic view being obtained, as the urethra closes just beyond the objective end of the tube. Thus, for the determination of the functional activity of the sphincter, for the estimation of its power of contraction, or of its degree of relaxation, particularly in the neurogenic disorders of micturition, the instrument is ideal. In the treatment and diagnosis of filiform strictures (fig. 8), the universal urethroscope should find a place in the armamentarium of ever urologist.

As a Kelly or Luys endoscope. Certain advantages are offered by the instrument in the presence of the large catheter outlet through which catheters or other devices may be introduced. For those who limit their work to the female urinary tract, the length of the instrument may be reduced from 7¼ inches to 6½ or 6¼ inches. The possibility of maintaining a dry field by aspiration through the tubule figure 2*d*, at the faucet figure 2*e*, obviates the necessity of introducing Kelly's special aspirating device.

As for its uses as an air inflation urethroscope or Elsner-Braasch cystoscope (fig. 4), enough has been said to indicate that it may be so employed, although we ourselves do not find any necessity for invoking the use of these methods.

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SOME NEW METHODS IN THE TREATMENT OF CARCINOMA OF THE LOWER GENITO-URINARY TRACT WITH RADIUM*

HUGH H. YOUNG and WILLIAM A. FRONTZ

From The James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

During the past two years, we have treated with radium sixty-six cases of cancer of the prostate. In forty-two of these, the tumor was extensive, not only the prostate but the seminal vesicles being involved. In nineteen the process was confined apparently to one half of the prostate and the corresponding vesicle, while in four the vesicles were apparently free from invasion.

The diagnosis of carcinoma was made by rectal examination alone in all but four cases. These had previously been operated upon, the tissue removed showing typical carcinoma. The diagnosis of malignancy was confirmed in twelve other cases, nine of which were subsequently operated upon and three coming to autopsy. In the remaining cases in which histological confirmation was impossible, the findings were typical of malignancy.

TECHNIQUE OF TREATMENT

The treatment in practically all of these cases has been carried out with 103.7 mgm. of radium element, contained in a thin glass tube 24.3 mm. in length and 3.4 mm. in diameter. In the treatment of all of the cases of prostatic carcinoma, the glass tube of radium has been contained in a capsule of platinum 29.5 mm. in length, 6.5 mm. in diameter and 1.5 mm. in thickness, a screenage more than sufficient to filter out practically all of the irritating beta rays. In the treatment of carcinoma of the prostate and seminal vesicles, three portals of application are available: the urethra, the bladder and the rectum. The platinum capsule with its contained radium is introduced in the beak of a metal instrument, in general outline not unlike the cystoscope[1] (fig. 1).

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* Read at the meeting of the American Urological Association in Chicago, April, 1917.

Urethra and bladder: The patient lies upon his back on a flat operating table and after the genitalia have been cleansed in a manner similar to that for cystoscopy, the instrument carrying the radium in its beak is introduced and held at the desired point by means of a mechanical arm attached to the table (see fig. 2). The prostatic urethra may be so treated that successive treatments do not overlap, the anterior half being treated at one time, the half nearest the bladder at another. The urethra, because of its anatomical relations to the tumor, forms an admirable point of attack and in cases with evident involvement of the lateral and median lobes, a large portion of the treatment is carried out from this site. The seminal vesicles and intervesicular region may be conveniently radiated through the bladder, the capsule being carried just within the internal sphincter and rotated to the right or left or allowed to remain in the mid line. In some of our cases, as much as five hours of radiation have been given during one seance, the position of the radium being changed at hourly intervals. We have made it a rule to chart as accurately as possible the exact position of a given radiation, as shown in the accompanying diagram (fig. 3). a straight line indicating the region radiated, opposite which is placed the date and the amount of treatment, reckoned in milligram-hours. By this means the treatment in a given case is graphically shown and too frequent repetition of radiation at one point may be

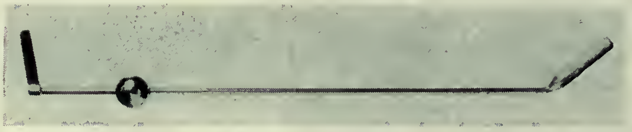

Fig. 1. Instrument for Rectal and Urethral Applications

avoided. The resistance of the bladder and urethra, so far as irritation is concerned, is subject to considerable individual variation, but as a rule from twelve to fifteen hundred milligram-hours may be given in the course of a month, providing radiation at any one point does not exceed 100 mgm.-hrs. during one treatment, and if the intervals between treatments are of sufficient length.

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* These instruments have previously been described in the Journal of the American Medical Association, April 21, 1917, by H. H. Y.

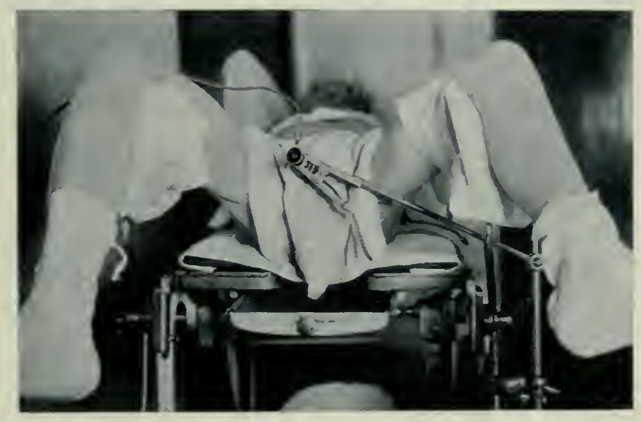

Fig. 2. Illustration Showing the Method of Giving Urethral and Bladder Radiations. The Mechanical Arm Attached to the Table Holds the Instrument in Desired Position

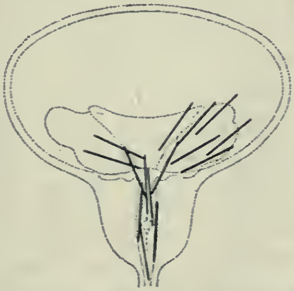

Fig. 3. Chart Showing the Transvesical and Transurethral Treatments

Rectal radiation. For these treatments, the patient lies upon his side, with the knees and thighs sharply flexed. The radium is introduced into the rectum in the beak of the instrument used for urethral applications and accurately placed over the part to be radiated, being held in position by the gloved finger until grasped by the mechanical arm (see fig. 4). It has been our plan before beginning treatment to chart as accurately as possible the outlines of the carcinoma. It is then possible, as shown in the accompanying diagram (fig. 5), to so plan the treatments as to avoid overlapping, thus decreasing the danger of rectal irritation. As many as fifteen to twenty areas may be thus mapped out and the entire tumor systematically treated. It is well in consecutive treatments to select areas quite widely separated, as for instance the seminal vesicles, or the apex of one lobe and the base of the other, thus reducing the danger of injury to the mucosa. The normal rectal mucosa is so freely movable over the underlying structures that the treatment of adjacent areas in rapid succession cannot be carried out without considerable risk.

In the trans-rectal treatments we usually endeavor to give from 1500 to 2000 mgm.-hrs. in the course of six weeks to two months, using the same precautions outlined above for the urethra. Usually at the end of this time, there are beginning signs of rectal irritation and the treatment is immediately discontinued, to be resumed some time after the last symptoms have disappeared which is usually in the course of one to two months. The rectal irritation produced by radium is manifested by frequent desire to stool, burning discomfort and the discharge of mucus which may be blood-tinged in the more aggravated cases. Rectal examination at this time may reveal considerable swelling of the mucous membrane or nothing abnormal may be made out. In certain cases having rather marked subjective symptoms, the mucous membrane may be normal to palpation, while in others, experiencing no discomfort whatsoever, the mucosa shows marked thickening. In one of our cases, palpation revealed in addition to marked thickening, definite crepitation as if there were air beneath the mucosa.

Great variation in the resistance of the mucous membrane has been noted. On the one hand, it may become quite marked after 500 to 800 mgm.-hrs. have been given, while in other cases from 1500 to 2000 mgm.-hrs., given in proportionately the same time are followed by little or no discomfort. The cause of this great variation in resistance is not always apparent but in our experience, carcinomatous involvement of the rectal wall or pressure upon the rectum resulting from marked enlargement of the prostate, suggests that interference with the blood supply and consequent diminution of regenerative power, may furnish an explanation. These are cases showing as a rule to palpation very little evidence of irritation. The rectal mucosa shows no thickening or ulceration, the chief symptoms being burning discomfort, frequent desire to stool and in some cases the occasional discharge of small amounts of mucus. The appearance

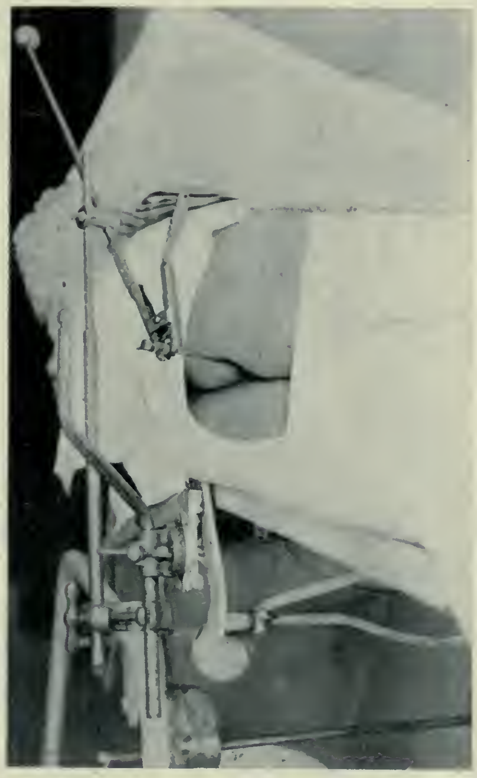

Fig. 4. Showing Method of Giving Rectal Radiations

of these symptoms, even though there be no palpatory evidence of irritation, calls for an immediate suspension of rectal treatment, the remaining course being carried out through the urethra and bladder.

Upon cessation of the treatment per rectum, slight symptoms of irritation usually subside in the course of a few weeks. From our experience it would not seem advisable to resume the treatment per rectum until two or possibly better three months after the last symptoms or other evidence of irritation through palpation have disappeared. Under the head of delayed reactions, may be grouped certain cases having only slight temporary irritation after the first series of treatments. Upon continuing the treatment after too short an interval, marked rectal irritation resulted, the appearance of severe irritation being long delayed, in some instances several months after the last treatment. In the majority of cases from 1500 to 2000 mgm.-hrs. of radium may be given during the course of six weeks to two months without producing marked irritation.

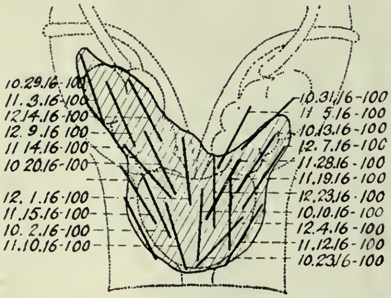

Fig. 5. A Case of Carcinoma of the Prostate and Left Seminal Vesicle (Right Vesicle Slightly Involved)

The radium treatments are here represented with dates, each line indicating 100 milligram-hours of treatment.

External radium treatments. Our study of these cases would be incomplete were we not to mention the external applications of large amounts of radium to the lower abdomen, perineum and sacrum. These treatments were carried out by Dr. C. F. Burnam. In three cases the treatment was purely external, no urethral or rectal applications being made and these have not been included in this series. In twelve other cases both methods were employed. The radiations were made with from 1500 to 2500 mgm., the duration of the treatment ranging from eight to fifteen hours and the distance from the skin averaging three inches. The three cases receiving external radiation alone showed no improvement. In the remaining twelve the improvement was marked in two cases. One of these was treated through the perineum with 2000 mgm. for nine hours at a distance of 3 inches. Subsequently he received 2600 mgm.-hrs. through the urethra and rectum. The consistence of the prostate was greatly reduced and the symptoms, which before treatment were greatly aggravated, cleared up completely. This patient remains symptomatically well today, one year after the treatment. The second case received two external applications and 900 mgm.-hrs. through the urethra. He was seen recently, eighteen months after the last treatment, with marked symptomatic improvement and a prostate somewhat enlarged but not suggestive of malignancy.

The chief difficulty in external treatments is the great distance of the radium from the lesion to be radiated. The distance is frequently from 15 to 25 cm., while in the internal treatments, particularly the urethral and rectal, it is possible to place the radium almost directly against the neoplasm, in fact separated only by tissues from 1 to 3 mm. thick (the urethral mucosa and the rectal wall). As the potency of the radium varies inversely as the square of the distance from the part to be radiated, the importance of reducing the distance can be appreciated.

STUDY OF RESULTS

The results from radium treatment of carcinoma of the prostate and seminal vesicles have in many cases been most encouraging. Cases presenting marked urinary obstruction have responded in the course of six weeks to two months and in some instances a large residual urine has diminished to zero. Cases giving a history of voiding from ten to twelve times at night and then only with extreme difficulty and pain, have shown, after a course of treatment marvelous improvement, urination being accomplished in a normal manner. In our series of sixty-six cases nineteen received less than 1200 mgm.-hrs., while the remaining forty-seven were given more than this amount, the radiation in many cases ranging from 3000 to 5000 mgm.-hrs. We have analyzed our results as follows:

Cases with complete retention. In eleven cases retention of urine was complete. In two cases the treatment was less than 1200 mgm.-hrs., while in the remainder it averaged about 3000 mgm.-hrs. The obstruction in these cases, with one exception, showed no improvement, eight of them subsequently coming to operation for the relief of urinary retention. The single case was only partially benefited and has had to resort to catheter at night since.

Frequency and pain. Fifty-one cases gave a history of more or less frequency and dysuria. In seventeen the radiation was less than 1200 mgm.-hrs. and the improvement symptomatically very slight. In the remaining cases, receiving adequate treatment, the improvement in many was very striking, nine being almost completely relieved of obstructive symptoms, nine showing marked improvement, nine responding only slightly, seven being unchanged.

Size and consistence. Those cases which have responded symptomatically have shown also, as a rule, improvement in the size and consistence of the prostate and seminal vesicles. In many instances the prostate has changed from a stony consistence to the normal elasticity. The size has also diminished although in this respect the change has not been so striking. In many of these cases, examination now would lead to a diagnosis of adenomatous hypertrophy. The change in the size and consistence of the seminal vesicles has not been at all comparable to the improvement noted in the prostate.

In the forty-two cases having extensive involvement, thirty received treatment exceeding 1200 mgm.-hrs. In eleven of these cases, all of which received from 2000 to 5000 mgm.-hrs., there was a marked change in the consistence, while in three the prostate showed considerable diminution in size and in four there were very definite changes in the size and consistence of the seminal vesicles.

Of the ninteen cases showing a unilateral involvement (prostate and one vesicle), fourteen received radiation exceeding 1200 mgm.-hrs. Of these receiving from 2000 to 4000 mgm.-hrs., eight showed marked softening of the prostate and in two there were corresponding changes in the vesicle.

In four of the cases the involvement was confined apparently to the prostate. In three of the cases the radium treatment was short and not completed and no conclusions can be drawn. In the fourth case, the carcinomatous area was small and confined to one lobe. Eighteen hundred mgm.-hrs. were given per rectum and 225 mgm.-hrs. per urethram during the course of ten months. At first there was apparent improvement in the consistence of the area but notwithstanding treatment it later assumed active growth and was completely removed by subtotal prostatectomy. No explanation for the unusual resistance in this case is apparent.

Of nineteen cases in which there was marked change in the consistence of the prostate, eight showed a striking improvement in urinary symptoms, four a moderate improvment, four slight improvement and three no improvement.

In five cases of the series the carcinoma was most resistant to treatment, there being very little change either in the size and consistence of the prostate and seminal vesicles and slight if any improvement in symptoms. One of these cases received radiation exceeding 2500 mgm.-hrs., two exceeding 3200 and two exceeding 5000.

In four cases a prostatectomy had been performed previous to the application of radium. The tissues removed at operation showed definite carcinoma. In two of these cases the treatment is too recent to draw any conclusions. In the third case a suprapubic prostatectomy was performed in January, 1915, in another city. From April 26, 1915, to May 12, 1915, nine radium treatments were given elsewhere through the rectum, the total radiation being 1800 mgm.-hrs. When seen by us in June, 1915, rectal examination revealed a prostate slightly smaller than normal, quite irregular, moderately indurated but not suggesting malignancy. The microscopic sections of the tissue removed at operation were examined by us and show typical carcinoma. On cystoscopy the trigone appeared thickened, very irregular and lobulated. On rectal examination, with the cystoscope in the urethra, the tissues in the trigonal region, although markedly thickened were extremely soft. Radium applications to the trigone were immediately begun June 10, 1915, and in the course of a few days 150 mgm.-hrs. were given. In addition an application of 1700 mgm. was given to the perineum and abdomen for a period of eleven hours. During the following month 160 mgm.-hrs. were given to the trigone and posterior urethra and 1600 mgm. were applied for four hours to the abdomen and five hours to the perineum. In October, 1915, the perineum was again radiated with 1900 mgm. for seven and a half hours. No treatment has been given since March, 1916, when he received 350 mgm.-hrs. to the trigone and urethra and 200 mgm.-hrs. through the rectum to the trigone. At the last cystoscopy ten months ago (June 10, 1916) the trigone was still considerably enlarged but the mucous membrane was smooth and there was nothing to suggest malignant invasion. Rectal examination was not suggestive of malignancy. This patient is free from symptoms at present (April 24, 1917).

In fourteen cases of the series with evident metastasis there was pain in the back, hips or thighs. In none of these cases, of course, was there any alleviation of this symptom following radiation of the primary growth. During the past six months we have had two cases complaining of marked pain in the hip and thigh which have been afforded considerable relief by intensive treatment with the *x*-ray, which was directed against the region involved in the spine or along the sciatic nerve, particularly in the region of the sacrosciatic notch. By using small portals side by side many exposures, all reaching the deep area involved, but each through a different skin area can be safely made. In a few cases with very severe pains in hip and thigh marked improvement was thus obtained. The Coolidge tube was used, operating at a spark gap of 9½ inches and a current of 20 milliamperes. A screen of 2.5 mm. of aluminum and 4 mm. of glass was employed. The usual distance from focus to skin was 8 inches and the time of exposure two and three-quarter minutes. The focal distance in all exposures was carefully measured and in the event of its being greater or less than 8 inches, the time was either increased or diminished, the time of exposure, other things being equal, being proportionate to the square of the distance of focus to skin. More or less recently we have been raying the abdomen, back and perineum in conjunction with the use of radium. We have endeavored in these cases to secure as many portals of entry as possible, the areas being plotted in 2 inch squares with a 10 per cent solution of silver nitrate which leaves a more or less permanent record. The radiation of a given area should usually not be repeated within a month's time. By following this plan we have seen no erythema following the treatment.

CASES SHOWING SYMPTOMATIC IMPROVEMENT

The following cases are cited as illustrative not only of marked symptomatic improvement but also of reduction in size and consistence of the prostate and seminal vesicles.

No. 5446, aged 80. Admitted October 12, 1916, complaining of frequent and difficult urination. For two years prior to his coming to the hospital he had had increasing frequency and for six months urination was accomplished with great difficulty and pain. Rectal examination on admission revealed a very definite carcinoma involving the entire prostate and left seminal vesicle. On cystoscopy 325 cc. of residual urine were recovered. Study of the prostatic orifice showed some median enlargement and considerable trabeculation of the bladder wall. From October 12, 1916, to December 16, 1916, 500 mgm.-hrs. of radium were given per urethram and 1500 per rectum. Examination at the end of this series of treatments showed marked improvement in the induration although the condition was still suggestive of carcinoma. Treatment was resumed January 8, 1917, and during the next three weeks, 500 mgm.-hrs. were given per urethram and 200 per rectum. At the present time (April 25, 1917) urination is accomplished with ease and the patient voids at normal intervals. There is no residual urine. Rectal examination reveals a prostate of normal size, smooth and slightly indurated. Both seminal vesicles are slightly thickened and adherent. The case now presents a picture of slight prostatitis and seminal vesiculitis.

No. 5193, aged 62. Admitted June 11, 1916, with a history of urinary frequency beginning three years before. These symptoms gradually became more marked and for the past year he has been required to pass his urine at hourly intervals during the day and from two to four times at night. Throughout the course of the illness there had been considerable hesitancy and dribbling and during the year before admission urination had been accomplished only after considerable straining.

Rectal examination showed that the prostate and seminal vesicles were involved in a very definite carcinoma. The prostate, although not much larger than normal, was very irregular, fixed, and markedly indurated, particularly the left lobe. The induration was continuous with a mass in the region of both seminal vesicles, both of which were enlarged, nodular, fixed and very hard.

The patient received two courses of treatments, the first being carried out between June 12, 1916, and July 20, 1916, during which time 1400 mgm.-hrs. of radium were given per rectum and 400 mgm.-hrs. per urethram. At the end of this series, the prostate and seminal vesicles showed very little change and the symptoms only slight improvement. The treatment was resumed in September, 1916, and from September 16 to October 14, 1916, 1000 mgm.-hrs. were given per rectum and 300 per urethram. At this time the patient complained of slight rectal irritation, examination showing a somewhat thickened rectal mucosa. The prostate was of normal size and everywhere elastic. Both seminal vesicles, although moderately prominent, were only slightly indurated. Rectal examination of the prostate and seminal vesicles if made now for the first time, would suggest the diagnosis of prostatitis and seminal vesiculitis, and not cancer. It has now been ten months since the beginning of this treatment. Since the last treatment in October, 1916, there has been gradual improvement. Urination is now (March, 1917) accomplished with ease, the patient holding his urine for three hours during the day and voiding twice at night.

No. 4726, aged 73. Admitted November 18, 1915, with a history of slight urinary frequency beginning one year previously. Shortly after the onset, urination became quite difficult. These symptoms gradually increased and for several months before admission the patient had been voiding every few minutes day and night. Finally complete retention requiring catheterization came on.

Rectal examination showed the prostate somewhat enlarged, its surface irregular and both lobes markedly indurated, the consistence of the left lobe being stony and undoubtedly cancerous. Both seminal vesicles were enlarged and indurated, the left apparently malignant, the right inflammatory. Cystoscopy: Residual urine 100 cc. Bladder capacity 150 cc. Both lateral lobes only slightly enlarged intravesically; moderate trabeculation of bladder wall and hypertrophy of trigone. Nothing suggesting carcinomatous invasion of bladder.

During the first month of treatment, the patient received 500 mgm.-hrs. to the urethra and bladder and one external radiation of 2000 mgm.-to the perineum—time nine hours, distance 3 inches. Treatment was resumed nine weeks later and during the next seven weeks 950 mgm.-hrs. were given per rectum and 825 per urethram. Frequent rectal examinations have shown gradual improvement in the condition and at the last examination in April 6, 1916, the prostate was not enlarged. The right lobe was somewhat irregular but perfectly elastic, while the left was smooth and still considerably indurated, but much less so than on admission. There has been no urinary difficulty since the treatment one year ago (letter Febuary 1917) and the patient is practically free from symptoms. Urination is perfectly normal and he is able to hold his urine for five hours.

THE HISTOLOGICAL CHANGES PRODUCED BY RADIUM

In twelve of the cases of carcinoma of the prostate and seminal vesicles, which had been subjected to more or less extensive radiation through the urethra and rectum, we secured tissue for histological examination. Of these cases nine were operated upon for the relief of urinary obstruction, eight having perineal prostatectomy performed, one the punch operation. In the remaining three tissue was procured at autopsy. Brief histories of these cases with clinical findings and treatment, together with gross and microscopic description of the tissue removed follows:

Case 1. No. 4766, aged 59. Admitted December 11, 1916, with a rather marked onset of urinary frequency eight months before. For several months the patient had been voiding every half hour at night and at fifteen-minute intervals during the day. Urination was accomplished only after marked straining, the urine being voided drop by drop. Several weeks before admission he developed complete retention, requiring catheterization. Examination on admission revealed an extensive carcinoma involving the entire prostate and seminal vesicles. On cystoscopy the lateral and median lobes showed slight hypertrophy intravesically. The trigone was very oedematous, irregular and elevated. There was no evidence of neoplastic growth within the bladder, yet the trigone gave the examiner the impression that it was infiltrated.

Treatment: Shortly after admission one external application of radium was made, 1886 mgm. being applied to the perineum for eight hours at a distance of 3 inches. During the next five months the patient received applications of radium to the prostatic urethra and bladder and per rectum, 100 mgm. of radium with a screenage of 1.5 mm. platinum being employed. Twenty-four treatments totalling 2900 mgm.-hrs. (1100 mgm.-hrs. per rectum and 1800 mgm.-hrs. per urethram and vesicam) were given. At the end of these treatments the symptoms so far as urination was concerned had not improved. Examination of the prostate, however, showed considerable improvement in the consistence, the gland being quite elastic. Slight changes in seminal vesicles. On May 20, 1916, a perineal prostatectomy was performed for the relief of urinary obstruction. The tissue removed at operation was of cartilaginous consistence, differing from the average carcinoma in the absence of the characteristic yellow color so frequently seen in malignant disease of the prostate.

Microscopically the tissue shows a large number of carcinomatous acini which are in various stages of degeneration. For the most part the arrangements is that of adenocarcinoma although in some areas the acinus is completely filled with cells. Most of the cells are broken away from the basement membrane, much shrunken and barely take the stain. All are very granular, a number being composed entirely of coarse granules surrounding the nucleus without any visible cell membrane. The nuclei which are of varying size are very pyknotic. In some areas the degeneration is complete, the outlines of the acinus being denuded of cells and filled with granular débris in which an occasional pyknotic nucleus is seen (see figs. 6 and 7).

Following the closure of the perineal wound rectal examination showed considerable induration in the region of the prostate with enlarged and indurated seminal vesicles. From August 9 to October 12, 2200 mgm.-hrs. of radium were given per rectum. At the end of these treatments rectal examination revealed slight induration in the region of the prostate and seminal vesicles but nothing suggestive of malignancy.

Case 2. No. 4231, aged 66. Admitted March 2, 1915, with a history of occasional attacks of acute retention requiring catheterization throughout a period of eighteen months. There was rather marked frequency and difficulty in voiding. Rectal examination, on admission revealed an extensive carcinoma involving the entire prostate and both seminal vesicles.

Treatment: The radium treatment in this case has been carried out by external application of large amounts and the intraurethral and intrarectal use of 103 mgm. The following external treatments were given:

April 28, 1915. 1200 mgm. to perineum for twelve hours.

May 11, 1915. 1700 mgm. to suprapubic region for six hours.

June 10, 1915. 1700 mgm. to perineum for five hours and 1700 mgm. to suprapubic region for four hours.

July 8, 1915. 1700 mgm. to suprapubic region for eight hours.

October 7, 1915. 2000 mgm. to suprapubic region for five hours and 2000 mgm. to perineum for five hours and 2000 mgm. to sacrum for five hours.

At the end of these treatments the patient showed very little change symptomatically and the prostate and seminal vesicles on rectal examination revealed practically the same condition as on admission. From this time until November, 1916, the treatments were carried out per urethram and and per rectum, a total of 3250 mgm.-hrs. being given (2500 per rectum and 750 per urethram). Examination now showed very little change in the size and consistence of the seminal vesicles. The patient's condition grew gradually worse and he developed complete retention of urine for which a perineal prostatectomy was performed in November 17, 1916.

Gross appearance. The tissue removed did not resemble carcinoma as it is usually seen. Much of it was quite soft, while other areas were fibrous and made up of interlacing trabeculae in the interstices of which were small yellow areas. The tissue was quite firm but not of stony consistence.

Microscopic. The sections of this tissue show adeno-carcinoma which in many places has extensively invaded the stroma. In many areas which are apparently carcinoma the acini are filled up with masses of material which take the hematoxylin stain and are composed of dense strands packed closely together. Whether this represents a peculiar type of nuclear degeneration or what appears more probable from a study of certain areas a fibro-blastic proliferation is difficult to determine. Among the strands may be seen epithelial nuclei. The epithelium for the most part shows marked degeneration although in certain areas it is fairly well preserved. In the acini containing none of the blue staining strands the cells are granular and take only a very slight hematoxylin stain. They are almost completely filled with oval nuclei in which the arrangement of chromatin is well made out. Throughout most of the section, however, the epithelium presents an appearance of more advanced degeneration; the cells are completely broken up but in some places pyknotic nuclei remain (see figs. 8 and 9).

Five weeks after the operation the patient left the hospital with the operative wound completely healed. He was able to retain urine for four to five hours and there was apparently an excellent functional result. Two months after returning home, however, there was a rapid extension of the carcinoma, the patient dying March 15, 1917.

Case 3. No. 4718, aged 61. Admitted November 15, 1915. This patient was admitted to the hospital with renal colic and during the routine examination a small markedly indurated area was found in the right prostatic lobe near the apex. He had never had any symptoms of urinary obstruction or symptoms suggestive of prostatic trouble. After the passage of the ureteral calculus radium treatment was begun, 103 mgm. of radium with 1.5 mm. platinum screen being given directly over the small area which apparently did not exceed 1.5 cm. in diameter. From February to November, 1916, eighteen treatments totalling 1800 mgm.-hrs. were given per rectum directly over the indurated area in the right lobe. Frequent rectal examinations showed a slight but definite increase in the size of the tumor, nothwithstanding the treatment, and on Febuary 9, 1917, a subtotal prostatectomy was performed, the carcinoma apparently being completely removed.

Gross appearance. Examination of the tissue removed showed a more or less localized carcinoma confined for the most part to the posterior capsule in the region of the apex. Little if any change as a result of radium could be determined from the gross appearance.

Microscopic. The sections apparently show no effect of radium treatment; the cells and nuclei are all well preserved and present nothing unusual. The tumor is very cellular, there being but a small amount of stroma present.

The patient was discharged from the hospital at the end of six weeks with the perineal wound healed. Urination was free and the patient was able to retain urine for five hours. Three months after operation a perineal abscess developed resulting in the formation of a recto-urethral fistula. Examination at the present time (May 15, 1917) reveals nothing to suggest recurrence.

Case 4. No. 5523, aged 65. Admitted November 9, 1916. The onset of urinary symptoms eight months prior to admission began with frequency and difficulty in voiding. These symptoms gradually became more marked until the patient developed a paradoxical incontinence. Rectal examination showed a somewhat irregular and very hard prostate. It was very fixed and the examining finger could not be passed between the lateral lobes in the mid line, as is usual in hypertrophy. The prostatic induration is continuous with a similar consistence in the region of both seminal vesicles, both of which are very much enlarged, irregular and adherent. During the next six weeks 900 mgm.-hrs. of radium were given per rectum and 400 mgm.-hrs. per urethram. The complete retention being unrelieved a perineal prostatectomy was performed December 17, 1916.

Gross appearance. The gross picture is rather characteristic of carcinoma except that it seems to contain more fibrous tissue and fewer yellow areas, although several definite yellow areas are to be seen. Instead of being incompressible, as is the average carcinoma, the tissue is quite elastic, a feature noted in other cases receiving radium treatments prior to operation.

Microscopic. These sections show a great excess of fibrous tissue in the meshes of which are acini which have undergone all stages of degeneration. The cells are pale-staining, coarsely granular and most of the nuclei completely pyknotic. The cell membranes have for the most part disappeared. The architecture of most of the acini is destroyed, no lumen being present, the cells being compressed by the dense fibrous tissue. It is impossible, therefore, to distinguish accurately between acini and true invasion. In several small areas of the section tubules filled with well preserved epithelial cells are seen. The cells are swollen, clear and contain active looking nuclei (a type of cell frequently seen when carcinoma is growing actively in a tubule). In one of these tubules several pseudo-acini can be seen, the cells being grouped about central lumina but without separating trabeculae. Except for these areas just noted, the tumor would appear to have undergone very marked regressive change (see figs. 10 and 11).

The operation was followed by closure of the perineal wound on the twenty-third day. At the time of his discharge from the hospital on Febuary 3, 1917, he was holding his urine for three hours during the day and voiding once at night. Urination was accomplished without straining and there was perfect control. Rectal examination at this time revealed nothing suspicious of malignancy.

Case 5. No. 5626, aged 58. Admitted December 30, 1916, with a history of obstructive symptoms beginning six months before. Frequency of urination and dysuria have gradually increased. Rectal examination on admission revealed a prostate somewhat enlarged, irregular, but elastic for the most part. Along the base of both lobes and the lateral margin of the left is rather marked induration which is continuous with an enlarged and hard left seminal vesicle. The condition was considered to be very suspicious of carcinoma and in the course of three weeks 800 mgm.-hrs. were given per rectum and 300 per urethram. At the end of this period the urinary retention was unrelieved and a perineal prostatectomy was performed.

Microscopic. A very cellular type of adeno-carcinoma. The acini are small and in most of the sections tightly wedged together, there being a very small amount of intervening stroma. In some of the sections the acini are so closely packed that the lumen is obliterated. The cells and nuclei show no apparent change due to radium.

The functional result in this case is excellent. The wound closed on the seventh day and at the time of his discharge from the hospital he was able to hold urine for four hours, voiding it freely and in good stream. Rectal examination revealed nothing to suggest malignancy.

Case 6. No. 4259, aged 65. Admitted March 17, 1915. This is a case of extensive carcinoma of the prostate and seminal vesicles. He was operated on March 24, 1915, for relief of urinary obstruction. He returned to the hospital October 4, 1916, with complete retention of urine. Examination revealed a marked extension of the carcinoma with infiltration of the prostatic orifice and trigone. Radium treatment was immediately begun and from October 5, 1916, to December 9, 1916, 2400 mgm.-hrs. were given per rectum and 250 per urethram. At the end of this time there was no improvement in obstruction. On December 13, 1916, through a perineal incision a large mass of carcinoma was removed from around the prostatic urethra and beneath the vesical orifice.

Microscopic. This tumor is apparently a very actively growing carcinoma. In some areas the arrangement is that of adeno-carcinoma. In others it has extensively invaded the stroma and conforms to no general type of architecture. The cells, in many areas, are well preserved; in others broken up. The nuclei in the adeno-carcinomatous parts for the most part are large, pale-staining and contain one or two nucleoli. The invasive growth shows marked pyknosis and some shrinkage of the cells away from the surrounding stroma. Apparently there has been no marked change as a result of radiation.

Case 7. No. 5298, aged 72. Admitted August 22, 1916. For two years prior to his admission to the hospital the patient had considerable urinary difficulty with frequent attacks of acute retention. Rectal examination, on admission, revealed a large carcinoma involving the entire prostate and both seminal vesicles.

Treatment. From August 26, 1916, to November 1, 1916, 1950 mgm.-hrs. of radium were given per rectum and 100 mgm.-hrs. per urethram. At the end of this time, there was no improvement in obstruction and a perineal prostatectomy was done for the relief of obstruction.

Microscopic. Sections of the tissue removed at operation show considerable fibrous tissue which is invaded by carcinoma in many places. This arrangement is that of adeno-carcinoma and the cells for the most part are very well preserved. In many areas are tubules which are filled with carcinoma cells which have a typical glandular arrangement. Many of the nuclei are pyknotic but there are no other evidences of any regressive change.

The postoperative course in this case was uneventful, the perineal wound closing at the end of four weeks. Urination was accomplished without diffculty, there was good control and the patient could retain his urine for four to five hours. On discharge from the hospital, December 8, 1916, there was moderate induration in the region of the prostate which also involved the seminal vesicles.

Case 8. No. 5418, aged 66. Admitted October 5, 1916. This history in this case dates back one and one-half years, at which time there was a sudden onset of urinary frequency and urgency. These symptoms have progressively grown worse and for eight weeks prior to admission the patient had been voiding every fifteen minutes during the day and had nocturnal incontinence. Examination on admission showed a very extensive carcinoma of the prostate and seminal vesicles. Residual urine 850 cc.

Treatment. From October 5, 1916, to November 22, 1916, 1400 mgm.-hrs. of radium were given per rectum and 300 per urethram. There was no improvement in obstruction and a perineal prostatectomy was done.

Microscopic. In none of the sections studied is there any change either in the cells or in the architecture of the tumor which can be ascribed to the action of radium. The tissue is typical of advanced carcinoma of the prostate.

The perineal wound in this case closed at the end of the third week, at which time the patient was retaining urine for four hours and voiding it without difficulty. Rectal examination on December 21, 1916, showed some induration in the region of the prostate but the seminal vesicle had diminished greatly in size and consistence.

Case 9. No. 2237, aged 61. Admitted September 4, 1915, with a history of urinary obstruction for six months. Examination on admission revealed carcinoma involving the right lobe and lower portion of right seminal vesicle. Radium treatments were immediately begun, the following external treatments being carried out.

September 15, 1915. 1965 mgm. applied to the perineum for ten hours at a distance of 4 inches.

October 6, 1915. 1580 mgm. applied to the perineum and back (sacrum) each for seven and one-half hours.

From September 15 to November 24, 1400 mgm.-hrs. were given through the urethra and bladder. As a result of this treatment, while there was very little symptomatic improvement, the prostate had diminished considerably both in size and consistence. On December 15 death occurred from a cardiac complication. Examination post mortem showed no invasion of the bladder, the carcinoma being confined to the posterior capsule and the right seminal vesicle.

Microscopic. The tissue which was removed at various levels shows typical carcinoma. The cells are for the most part quite well preserved and only rarely conform to the adeno-carcinoma arrangement. They are present in long strands between bundles of fibrous tissue which predominates. In many areas the cells are broken up and the nuclei pyknotic. The tumor, however, gives one the impression of being actively growing and only slight degenerative changes can be seen.

Case 10. No. 4954, aged 77. Admitted March 13, 1916, with a history of urinary obstruction for five years. For two years previous to admission he had been voiding from ten to twelve times at night. Examination revealed an extensive carcinoma involving the entire prostate and seminal vesicles. Residual urine 250 cc.

Treatment. From March 13 to April 1, 1800 mgm.-hrs. of radium were given per rectum and 300 mgm.-hrs. per urethram. At the end of this series of treatments the symptomatic improvement was remarkable, urination being normal in every respect. Rectal examination showed no evidence of prostatic induration and one examining the prostate for the first time would say that the prostate was somewhat enlarged and somewhat characteristic of adenomatous hypertrophy but not all suspicious of carcinoma. Examination of the seminal vesicles, however, showed very little change. They were still about the same size as formerly but had softened somewhat under the treatment Because of rectal irritation, treatment was suspended until June 3. Cystoscopy at this time revealed no residual urine and no evidence of carcinomatous invasion of the bladder. The patient still remained free from urinary symptoms. Radium treatment was resumed and from June 3 to July 18, 700 mgm.-hrs. were given per rectum. The patient remained free from symptoms until September 20, when he noticed the escape of urine per rectum. On admission to the hospital on October 4, examination revealed a great extension of the carcinoma which had ulcerated through the posterior wall of the bladder and rectum with the formation of a recto-vesical fistula. Death December 15. Autopsy.

Microscopic. Sections of the tissue show definite carcinoma in every portion of the prostate. The tumor is very cellular and the stroma which is relatively slight in amount is everywhere invaded. The carcinoma cells are found tightly pressed together in large clusters and the glandular arrangement is rarely seen. The cells, for the most part, are well preserved and the radium had produced apparently no change in the microscopic appearance of the tumor.

Case 11. No. 5170, aged 67. Admitted June 1, 1916, with a history of urinary frequency for one and one-half years. For two months before admission he had been voiding three to four times at night. Examination on admission revealed an extensive carcinoma of the prostate and both seminal vesicles.

Treatment. Radium treatment was begun immediately and during the first six weeks he received 1400 mgm.-hrs. per rectum. He returned to the hospital in September, examination showing a marked extension of the growth with metastases to the spine. Death November 4, 1916.

Microscopic. The sections which were made from all portions of the prostate show typical carcinoma. The carcinoma cells are well preserved and no changes due to radium can be demonstrated.

Case 12. No. 5299, aged 72. Admitted August 22, 1916. This patient gave a history of urinary frequency and difficulty in voiding for three years. For a month before admission, he had been catheterized once or twice daily, the residual urine being from 500 to 800 cc. Examination at the time of admission revealed a definite carcinoma of the prostate with questionable involvement of the seminal vesicles. The residual urine was 450 cc. and cystoscopy showed marked irregularity of the prostatic orifice suggesting carcinomatous invasion.

Treatment. During the first series of treatments from August 22 to October 3, 1700 mgm.-hrs. were given per rectum and 200 mgm.-hrs. per urethram. At this time there was slight symptomatic improvement and general softening of the gland. The second series of treatments began December 4. From this time to January 2, 100 mgm.-hrs. were given per rectum and 200 per urethram. Symptomatically there was very slight if any improvement, the residual urine remaining the same and on January 15, a punch operation was done for the relief of urinary obstruction. This was followed by a good functional result and the patient has been voiding freely ever since.

Microscopic. Examination of the tissue removed at operation shows definite adeno-carcinoma. No changes in the sections can be ascribed to the action of radium.

Remarks. As to the great diversity of clinical effect and cellular change produced by the radium treatments given in the preceding cases, we have no explanation to offer. We have given at length the good with the bad results.

RADIUM TREATMENT OF BLADDER TUMORS

In the application of radium to bladder tumors the patient is prepared as for cystoscopy. For tumors in the region of the vesical orifice and trigone, an instrument very similar to that employed for the treatment of prostatic carcinoma is used. It is, however, a tubular instrument through which an observation cystoscope can be passed, thus enabling the operator to apply the radium accurately to the tumor (see figs. 12, 13 and 14). For tumors upon the anterior and lateral walls, the instrument just described is sometimes unsatisfactory as the tip of the radium capsule and not the long diameter comes in contact with the tumor. To obviate this difficulty, another type of instrument was devised, as shown in figures 15, 16 and 17. It is seen to possess a beak composed of two hollow halves, and an intermediate shell in which the capsule containing the radium is placed. By a simple screw mechanism, the halves can be separated and thus the shell containing the radium swung out so that its long axis lies parallel to the shaft of the instrument. This instrument also carries a cystoscope making accurate applications possible. Neither of the above instruments is suitable for some tumors lying on the posterior wall. For the treatment of these another design was necessary (see figs. 18 and 19). This will be seen to resemble in general outline the instrument first described except that its beak, which is fenestrated, serves as a capsule for the radium. By means of wires concealed in the shaft of the instrument this beak

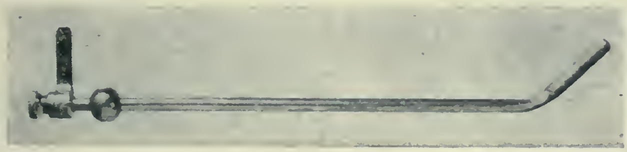

FIG. 12. INSTRUMENT USED FOR TUMORS IN THE REGION OF THE VESICAL ORIFICE AND TRIGONE

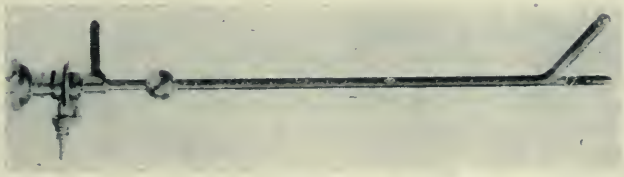

FIG. 13. THE SAME AS FIGURE 12 WITH THE OBSERVATION CYSTOSCOPE IN POSITION

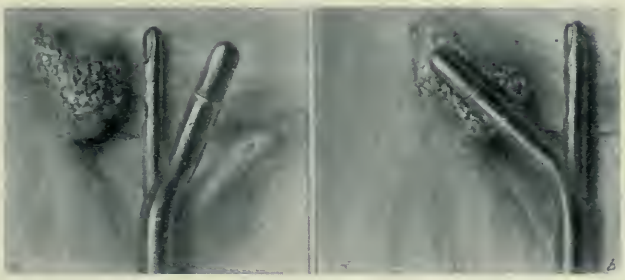

FIG. 14. SHOWING THE APPLICATION OF RADIUM TO A TUMOR IN THE REGION OF THE RIGHT URETERAL ORIFICE

can be made to revolve about its center so that its long axis can be brought to a point at right angles to the long axis of the instrument. The radium can thus be placed broadside upon the tumor (see figs. 20 and 21).

In carrying out these treatments we have usually employed a capsule of brass, one side of which is fenestrated, the diameter of the fenestra being about one-third the circumference of the capsule. Both the beta and gamma rays are thus utilized, the fenestrated surface of the capsule being placed directly upon the tumor.

As in treatment of carcinoma of the prostate, it has been our plan to map out the area to be treated and to outline each treatment together with the date and dose given (see fig. 22). After the radium has been carried to the desired point the instrument is held in a fixed position by the mechanical arm employed in the treatments described for carcinoma of the prostate. The length and frequency of the treatments varies considerably with the individual case, but as a rule the radiations can be given for a period of an hour once or twice a week.

This report includes forty-five cases of tumor of the bladder treated with radium alone or a combination of radium and fulguration. Of these cases fifteen were papillomata, thirty carcinomata. Of the papillomata only two were treated with radium alone, the one receiving 350 mgm.-hrs., the other 50 mgm.-hrs. Both tumors disappeared within three weeks after radiation.

In thirteen cases of papilloma a combination of radium and fulguration was employed. In seven cases the actual effect of the radium cannot be stated. The tumors disappeared but it is possible that many would have responded to fulguration alone. In the remaining 6, however, the radium played apparently a very definite rôle and it is with a consideration of these cases that we are chiefly concerned. These were all papillary, pedunculated tumors, presenting cystoscopic appearances similar to the type of tumor which usually responds to fulguration. In two of these cases specimens were obtained with our cystoscopic Rongeur. Both sections showed histologically malignant change in the periphery of the tumor without infiltration, the changes being entirely in the epithelium, there being no evidence of infiltration of the axis of the papilla. In these six cases, the tumors were first treated by fulguration and in all of them the response was either entirely negative or

Fig. 15. Instrument for the Treatment of Lateral Wall Tumors

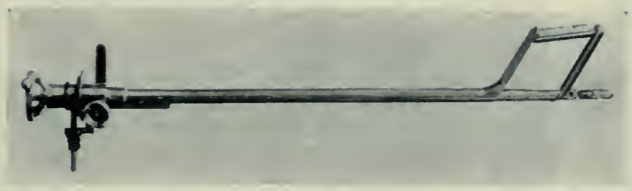

Fig. 16. Instrument Shown in Figure 15 with the Blades Open. Observation Cystoscope in Position

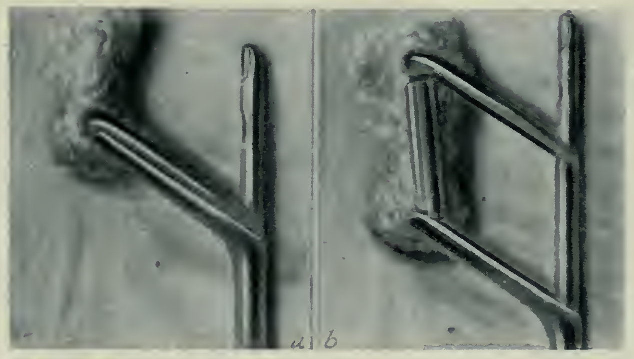

Fig. 17. Showing Application of Radium to the Tumor

extremely slow. Following a fulguration the tumor might appear as a charred mass and it would seem certain that complete destruction had been effected; yet, upon cystoscopy ten days or two weeks later, the tumor would appear clean, active and of approximately its original size. Repeated fulguration met with the same result although in one of the cases, the treatment was carried out at two-weekly intervals over a period of six months with practically negative results. Radium was then applied directly to the tumor, from 200 to 600 mgm.-hrs. being given. So far as could be determined there was little if any cystoscopic change as a result of the radiation. Upon returning to fulguration, however, the response was very prompt, the tumor disappearing in one to three treatments.

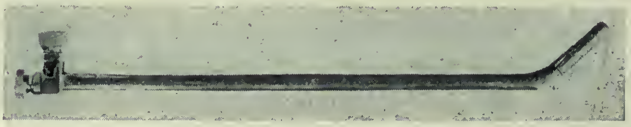

Fig. 18. Instrument for the Treatment of Anterior and Posterior Wall Tumors

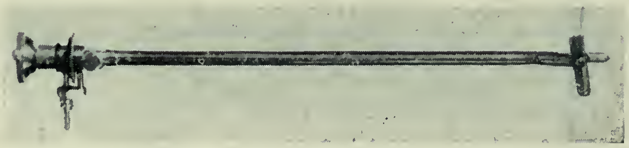

Fig. 19. The Instrument Shown in Figure 18 with the Beak Turned Ready for Application to the Tumor

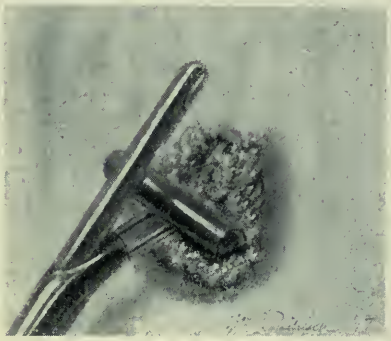

Fig. 20. Application of Radium to the Tumor

The following cases are examples of the type of papilloma resisting fulguration, responding promptly, however, to this method of treatment after radiation.

Case 1. No. 4894, aged 72. Admitted April 23, 1915, giving a history of hematuria for several months. On cystoscopic examination a tumor about 1 inch in diameter was seen back of the right ureteral orifice. The tumor did not project markedly into the bladder, was rather pink in color and the papillae short and stubby. From the cystoscopic appearance alone, it was difficult to rule out an early papillary carcinoma.

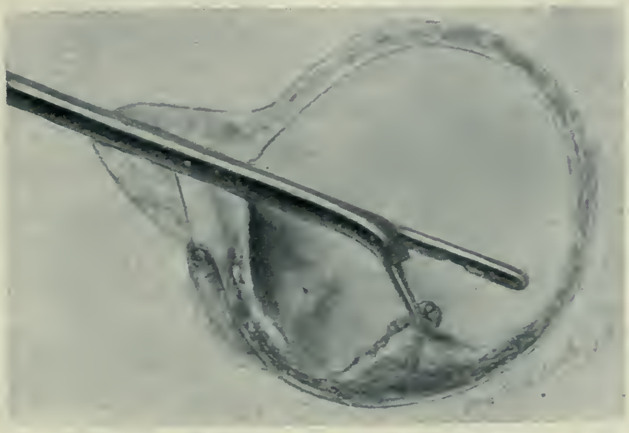

Fig. 21. Sagittal Section of Bladder Showing the Application of Radium to a Tumor on the Posterior Wall

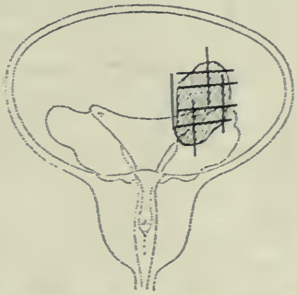

Fig. 22. Chart Showing Tumor in Region of Left Ureteral Orifice, the Straight Lines Each Indicating 100 Milligram-Hours Radiation

From a specimen obtained with our Rongeur, histological sections were made showing the ordinary malignant papilloma without infiltration, there being no invasion of the axis of the papillae, the malignant changes being confined to the epithelium alone. Fulgurations were begun at weekly intervals and continued over a period of six months. The tumor appeared very resistant and at the end of six months it was at least three-fourths its original size. The tumor at times was vigorously fulgurated so that it appeared as a charred, blackened mass, yet upon returning two weeks later nothing would suggest that any treatment had been carried out. Patient was then given six applications of radium of one hour each (600 mgm.-hrs.) during a period of about eight weeks. In these applications the fenestrated capsule was used, thus utilizing both the beta and gamma rays. At the end of this treatment, the tumor appeared possibly slightly smaller but the change was not striking. Fulguration was then resumed, the tumor was thoroughly charred and when the patient returned for examination ten days later the cystoscope showed the tumor had completely disappeared. No other treatment was given. Six months later the patient died of pneumonia. Examination of the bladder post-mortem showed no evidence of recurrence; the mucous membrane was smooth and section showed no evidence of cancer and the pelvic organs were negative for metastasis.

Case 2. No. 5244, aged 71. Admitted July 17, 1916. This patient gave a history of hematuria beginning four years before. Because of marked bleeding and consequent urinary difficulty suprapubic cystostomy was done a few months after the onset symptoms. At operation a bladder tumor was found which was treated frequently by fulguration without result until admission to the hospital. Cystoscopy showed a large, lobular, irregular tumor occupying the right lateral wall. The tumor was clean, there being no areas of necrosis and the adjacent mucous membrane normal. From July 18 to August 3, patient received four radiations to the tumor, totalling 200 mgm.-hrs. The treatment was resumed August 17 and from this time until September 23 five radiations totalling 300 mgm.-hrs. were given. Fulguration was then begun, the tumor disappearing after two applications. This patient was last seen Febuary 8, 1917, at which time he was entirely free from urinary symptoms. Cystoscopy at this time showed no evidence of recurrence.

Carcinoma of the bladder. Our results of radium treatment of the infiltrating type of malignant tumor, from a curative standpoint, are most unsatisfactory. In our series of thirty cases, in no instance was there any evident response to the radium, nor so far as we could determine was fulguration influenced by preceding radiation as in the tumors just mentioned. In a few instances hemorrhage has been controlled and in one case with extensive involvement in the region of the vesical orifice there was marked improvement in urination. The application of radium in these cases has been made directly to the tumor and in cases with trigonal and posterior-wall involvement rectal radiation has been employed.

CONCLUSIONS

The use of radium in the treatment of carcinoma of the prostate and seminal vesicles in many cases has resulted not only in marked symptomatic improvement but in definite reduction in the size and consistence of the tumor. In several of the treated cases subsequently coming to operation it has been possible to secure prostatic tissue for microscopic study. Some of the adequately treated tumors (those obtaining from 1200 to 4000 mgm.-hrs.) show extensive destruction of the cancer cells throughout large areas. In other areas the general architecture of the tumor is altered and the cells and nuclei appear in varying stages of degeneration. The histological change in several of these tumors is most encouraging and it seems probable that radium treatment may have a distinctly curative effect in some of them.

The internal use of radium either by urethra or bladder or by rectum, by accurate methods of control and fixation, would seem to be productive of far better results than the employment of much larger amounts externally, the chief difficulty of the latter method being the greater distance between the portal of application and the tumor.

The irritating effect of radium, which was formerly the great objection to its use in the urethra and rectum, can be avoided by the accurate methods of use which we have introduced and if the dose is carefully regulated and if care is used to avoid too frequent application to any one spot. The discontinuance of treatment at the first sign of rectal irritation cannot be too strongly emphasized, for if the treatment be carried beyond this point serious burns may result. Frequent rectal examinations may reveal a thickened rectal mucosa which may be the first evidence of irritation. With the onset of rectal irritation the urethral and vesical radiation may be substituted. The urethral and vesical mucosa is apparently quite resistant to the action of radium and in our series no ill effect has been noted following intensive treatment from these points. In these cases, however, it is well to mention that we have always employed a screen of 1.5 mm. of platinum.

The determination of a safe interval between the disappearance of rectal symptoms and the resumption of treatment will vary with the individual case, the severity of the symptoms, their duration, the amount of radiation producing the original irritation and the character of the rectal mucosa. Cases having had rather severe and prolonged symptoms should be held for two to three months before rectal treatment is resumed. Where large amounts of radiation have been tolerated, finally resulting in more or less irritation, the interval between the disappearance of symptoms and the resumption of treatment should be much longer than in those cases showing evidence of irritation after a few hundred milligram-hours.

The results obtained in the radium treatment of bladder tumors have been most satisfactory in the malignant papilloma type which have failed to respond to fulguration. Certain of these cases have resisted most stubbornly the high frequency treatment, but finally responding promptly to it after a few hundred milligram-hours of radium. In our hands the treatment with radium of the infiltrating types of malignant tumor has been less encouraging and in no case in which there was definite infiltration of the bladder wall, as demonstrated either by cystoscopy or by rectal palpation, has a cure been effected.

In radium we undoubtedly have a most potent agent capable of producing marked changes in malignant tumors as shown both by physical and microscopic examination. That some cases may be completely cured seems probable, though more time must elapse before accurate final determinations can be made.

It seems to be proven beyond doubt that close apposition of radium to tumor is very desirable, and that really marvelous absorption of infiltration, disappearance of induration and reduction to normal size and consistence may occur in even extensive cases of cancer of the prostate and seminal vesicles by the accurate instrumental methods here employed.

PLATES

PLATE 1

FIG. 6. Low power view of section of prostate (case 1) showing degenerative changes.

FIG. 7. High power view of section of prostate (case 1) showing extensive destruction of cancer area.

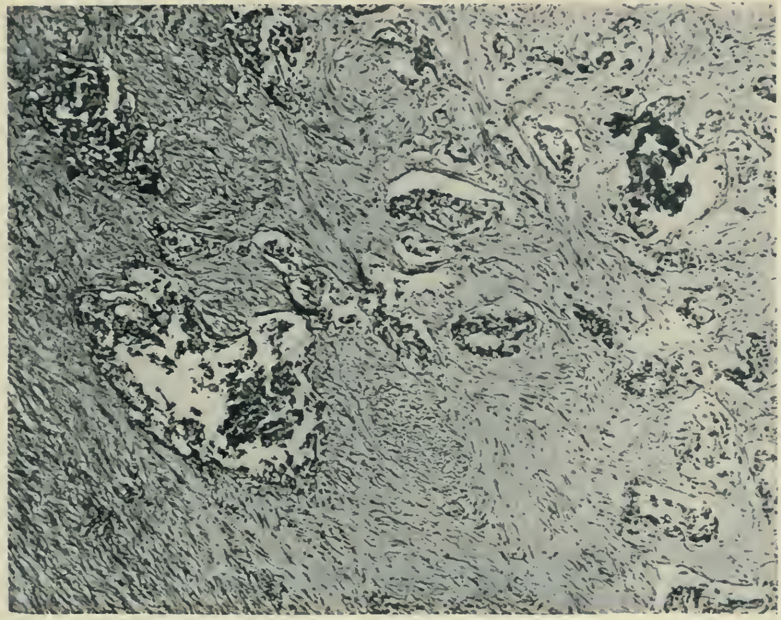

Fig. 6

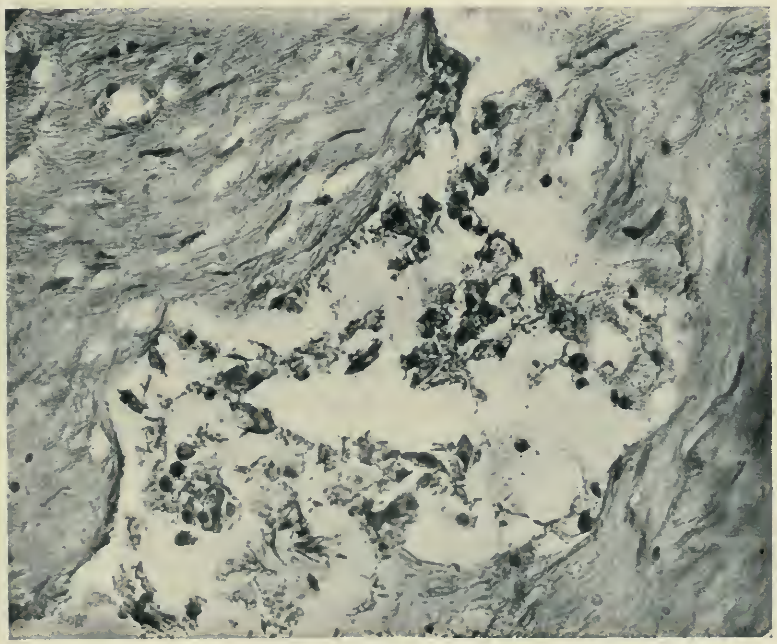

Fig. 7

PLATE 2

Fig. 8. Low power view of case 2 showing peculiar nuclear changes.

Fig. 9. High power view of area shown in figure 8.

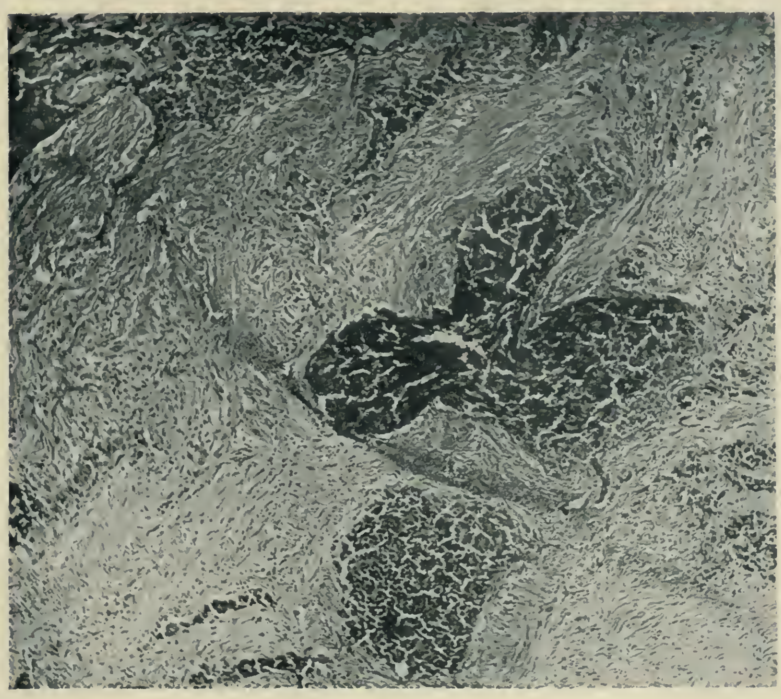

Fig. 8

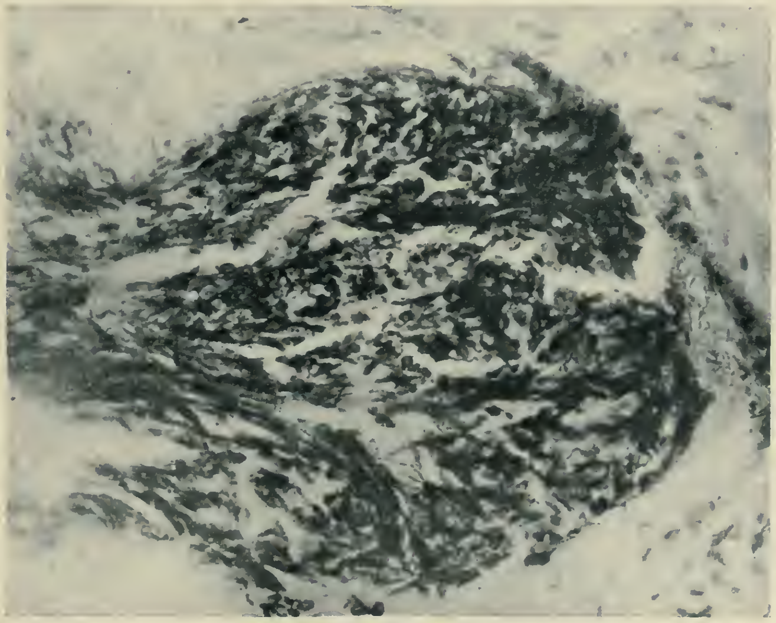

Fig. 9

PLATE 3

Fig. 10. High power view of section from case 4, showing one of the small areas of carcinoma apparently unaffected by the treatment.

Fig. 11. High power view of section of case 4, showing marked degenerative changes seen through most of the tumor.

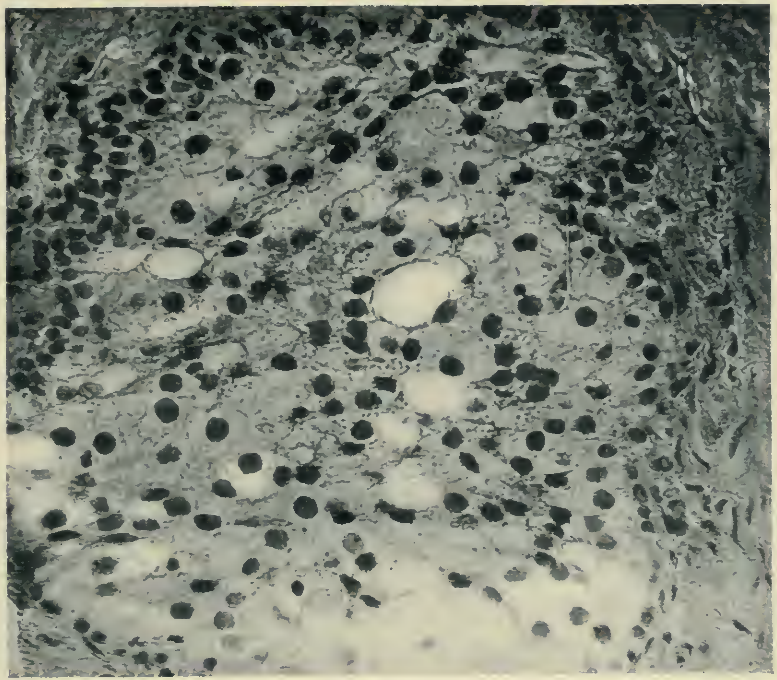

Fig. 10

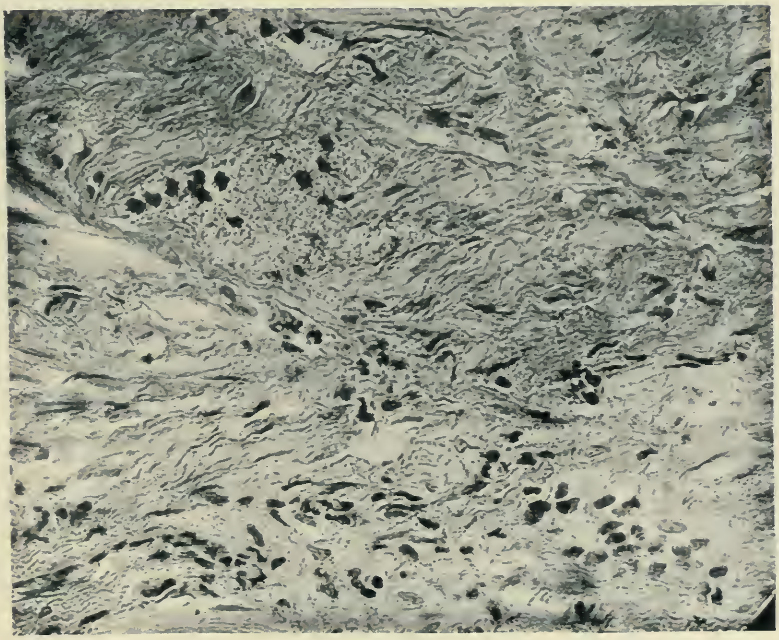

Fig. 11

A STUDY OF THE VESICAL ORIFICE FOLLOWING PERINEAL PROSTATECTOMY

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The readjustment of the musculature about the neck of the bladder following prostatectomy is still somewhat imperfectly understood, and it is only during the last ten years that this phase of prostatic study has received really any attention. In fact, previous to that time there are scarcely any recorded observations upon the subject of the resulting anatomical conditions about the vesical neck and prostatic urethra following prostatectomy. In recent years, however, when surgeons are taking a much keener interest in the ultimate results of their work, we find numerous references to the final condition of the musculature about the bladder orifice after operative interference. Even with this added interest, the amount of careful study upon the subject is still surprisingly small and with the exception of the work of Hyman in 1914 on the changes at the bladder outlet following suprapubic prostatectomy, there is practically no adequate study of the subject.

Wallace (1) in 1907, quoting Thompson Walker, who examined a case two years after suprapubic prostatectomy, states,

> In this instance a cavity, the size of a hazel nut, remained at the site of the prostatectomy. Thompson Walker considered that the internal sphincter in this case had remained dilated and consequently hardly likely to perform its function as a sphincter.

Freyer (2) in 1908 in the report of an autopsy on a patient dying twenty-two days after suprapubic prostatectomy found the posterior urethra funnel-shaped and continuous with the bladder cavity, the bladder really terminating in the region of the triangular ligament at the compressor urethrae muscle.

Wallace and Page (3) in 1911 show a cystogram taken after the injection of a suspension of bismuth into the bladder of an individual who had had a suprapubic prostatectomy. From their description the plate "shows the bladder cavity continuous with the cavity from which the prostatic adenoma was removed." They state that the adenomatous hypertrophy of the prostate frequently pushes aside and stretches the internal sphincter to the extent of rendering it probably useless, and that after its removal suprapubically "the sphincter remains a patent ring." They further add that cystoscopic examination through the supra-pubic wound sometime after prostatectomy has frequently shown a small pouch still present at the site from which the hypertrophied lobes were removed.

Wade (4) in 1914 in an extensively illustrated article shows several photo-micrographs of cross sections of the vesical neck and prostatic cavity made from autopsy specimens removed sometime after suprapubic prostatectomy. In these the internal vesical sphincter has remained dilated. He states that when the prostate possesses the gross structure and relationships of the normal organ, its suprapubic removal necessitates the division of the internal vesical sphincter.

Hyman (5) in 1914 presented a very comprehensive study of the normal bladder and its sphincters and particularly the changes that were brought about at the orifice following suprapubic prostatectomy. His work was done by means of radiographs taken of the normal bladder and of the bladders in cases of prostatic hypertrophy before and at varying intervals after operation. In his work he used a 5 per cent solution of collargol, introduced into the bladder through a catheter which was withdrawn before the radiograph was taken. In all of his normal bladders the internal sphincter was found to be the point of closure. This was also the case in prostatic hypertrophy previous to operation.

Of thirty-eight cases studied after suprapubic prostatectomy, Hyman found that twenty-eight showed two distinct cavities, the bladder cavity and continuous with it the one resulting from the removal of the adenomatous portion of the prostate. A few of the remaining showed only a very slight funnel formation in the region of the prostatic urethra continuous with the bladder cavity and the rest showed no change from the normal. He concluded that the internal sphincter marked the site of closure in the normal bladder and also in the bladder of prostatic hypertrophy. After suprapubic prostatectomy, however, the external sphincter or compressor urethrae forms the point of bladder closure in the majority of cases, the internal sphincter or normal closing muscle of the bladder having been destroyed or rendered useless by operation. He further concluded that the interval after operation made no difference in the relaxed condition of the internal sphincter.

In view of the almost uniform dilatation of the internal sphincter following suprapubic prostatectomy, it seemed interesting to investigate the condition of this region following the operation by the perineal route. For this study twenty-five cases were taken at random from the clinic of The James Buchanan Brady Urological Institute and from thé private practice of Dr. Hugh H. Young. The operation in every instance has been the Young conservative perineal prostatectomy (6).

The study of the vesical orifice was made in these cases by means of cystograms taken at varying periods after operation, i.e., three weeks to thirteen years. These were made after filling the bladder with a ten per cent thorium solution as recommended by Burns (7). It has been possible from these radiographs to study the bladder ouline, particularly the region of the prostatic orifice, for evidence of dilatation as shown by the escape of thorium into the posterior urethra.

In the study of twenty-five cases, in no instance did the internal sphincter remain permanently dilated and it seems probable that following perineal prostatectomy, the musculature about the vesical orifice becomes readjusted in the vast majority of cases. This occurs in some instances as early as the third week after operation and probably remains so throughout life, as shown in one of the cases in which the internal sphincter was functioning normally thirteen years after operation.

One very interesting case in the series was incontinent for twenty months after operation, the cystogram showing definite dilatation of the internal sphincter after fourteen months. At the end of twenty months the patient regained urinary control and the cystogram revealed an internal sphincter tightly closed. Referring to the operative note of this case, the prostatic orifice lay very deep, and to facilitate the removal of a very adherent median lobe, the margins of the orifice were grasped with clamps, and the structure pulled into the wound. The trauma produced by this procedure very probably explains, partially at least, the long continued incontinence. It is interesting, however, to note that even after twenty months there was complete restoration of function.

From the early work of Rehfish (8), who first demonstrated that the internal sphincter marked the normal closing point of the bladder, and also from the contributions of Born (9), Kohlrausch (10), Barkow (11), and Henle (12), and the more recent observations of Völcker and Lichtenberg (13), Leedham-Greene (14), Barringer and MacKee (15), Uhle (16) and Hyman, it has been well established that the point of closure in the normal bladder, even when under great distention, is at the internal sphincter. However, it is a well known fact that the internal sphincter can be removed or destroyed without resulting in incontinence.

This has been demonstrated by Young (17) in cases in which the neck of the bladder and entire prostate have been resected for malignant disease. The destruction of the internal sphincter in some cases or suprapubic prostatectomy has also proven this point. Cecil (18), in an excellent presentation of the subject, has recently given us a very comprehensive review of the factors concerned in the mechanism of bladder closure. He concludes that either the external or internal sphincter may be destroyed without interfering with the function of retention of urine, providing the remaining muscle is in a normal condition.

The whole question of whether the closure of the bladder takes place at the internal sphincter or external sphincter may seem to be rather a minor matter, particularly if perfect urinary control exists. However, after operations about the vesical orifice, if the internal sphincter can be restored to its normal function, such a result is surely more desirable, for in such a case the possibility of incontinence is definitely eliminated. Furthermore in the event of dilatation of the internal sphincter, the prostatic urethra becomes practically a part of the bladder cavity. Ejaculation therefore occurs into the bladder, thus diminishing if not entirely preventing the possibility of fertilization.

From the observations of Wallace and Hyman it has been shown that, in most cases of suprapubic prostatectomy, the internal sphincter is so damaged that it is useless as a sphincter muscle and thereafter the external sphincter forms the closing point of the bladder. Following this operation, there is usually no incontinence and the external sphincter is apparently adequate for a condition of perfect urinary continence.

The part played by the internal and external sphincters and also by the unstriped intrinsic musculature of the posterior urethra situated between the two with their inter-relations is not as yet clearly known. The intrinsic muscles of the urethra, while not usually accorded much clinical significance, are probably quite important. They are very definite structures, involuntary in type, and situated for the most part along the prostatic and membranous urethra. They are derived from the musculature of the trigone and consist of two layers, (1) an inner longitudinal, (2) and an outer circular layer. The former, which is very thin but more widely distributed, can be traced from the scattered longitudinal fibers of the trigone down beneath the internal sphincter as far as the openings of the ducts from Cowper's glands. The outer coat arises from the circular layer of the trigone, continuing as far as the termination of the membranous urethra. The latter are more numerous than the longitudinal fibers and at the vesical orifice are massed into a circular band several layers thick. Both of these layers are of the variety of smooth muscle and are innervated, together with the internal sphincter itself, by branches from the prostatic and cavernous plexuses through the hypogastric plexus, inferior mesenteric ganglion and ganglia of the sympathetic. The external sphincter, on the other hand, is a voluntary muscle, innervated by branches of the internal pudic. It consists chiefly of fibers arranged in circular form lying between the layers of the triangular ligament but a few strands originate at the apex of the prostate and scantily surround the membranous urethra.

Normally the involuntary muscles about the vesical orifice, namely the internal sphincter forms the point of bladder closure. After destruction of the internal sphincter however incontinence does not always result. It is hardly conceivable that the external sphincter which is purely a voluntary muscle explains the ability to retain urine in these cases and it is probable that the remaining intrinsic musculature of the prostatic and membranous urethra plays a very definite rôle in preserving this function. The rare cases of incontinence following suprapubic prostatectomy are probably instances where in addition to destruction of the internal sphincter, so much of the urethra has been injured as to render useless its involuntary musculature.

The cystoscopic changes in tabes dorsalis together with the clinical picture presented would seem to afford another illustration of the important rôle played by these intrinsic muscles.

This disease involving as it does the dorsal columns of the cord, destroys the nerves innervating smooth muscle, in other words, the sympathetic fibers. The dilated, atrophic, trabeculated bladder with a small, flat trigone and ureteral openings that fail to contract on functioning form a well known picture. At a relatively early period of the disease there is a definite involvement of the internal sphincter causing a relaxation at the vesical orifice. This is of varying extent according to the degree of nervous involvement. At first there is only slight dilatation of the vesical sphincter, the posterior urethra being normal and with this slight dilatation there is practically never incontinence. From this initial stage there are varying degrees of involvement extending to the prostatic urethra destroying more and more fibers innervating the intrinsic musculature until a funnel-shaped posterior urethra is the result. This shows involvement of practically all the nerves to the involuntary intrinsic muscles, which condition always results in incontinence. The stages between these two pictures may give a varying degree of continence depending upon the degree of involvement of the internal sphincter and intrinsic muscles of the posterior urethra and not on the involvement of the internal sphincter alone. In this disease the motor nerves are uninvolved and the innervation of the external sphincter through branches of the internal pudic is unharmed, though with this muscle normally innervated it would not seem to be sufficient to give urinary control when all the involuntary fibers posterior to it are destroyed.

Following perineal prostatectomy, the point of bladder closure is at its normal site in every instance, i.e., the internal sphincter. This returns to normal in some cases less than one month after operation and even earlier judging from the clinical evidence of urinary continence of one to two hours duration a few days after perineal prostatectomy when an external urethrotomy has been performed in the membranous urethra, back of the external sphincter.

In those cases of incontinence following perineal prostatectomy the internal sphincter has always been injured either as the result of long standing distension by greatly hypertrophied lobes or at the time of operation. This however is insufficient to account for the condition and it would seem that the external urethrotomy with its varying amount of damage to the intrinsic involuntary musculature of the membranous urethra coupled with the destruction of the intrinsic prostatic and internal sphincter muscles is the anatomical explanation of these cases. In such cases the external sphincter may be destroyed though the question of continence would seem to rest on the preservation of the involuntary muscle fibers.

SUMMARY

1. Following a perineal prostatectomy the internal sphincter returns to normal in practically every instance. This usually occurs in a period of a few weeks as demonstrated by thorium cystograms.

2. The internal sphincter may return to normal even when dilated for a period of over a year.

I desire to thank Dr. Hugh H. Young, director of the James Buchanan Brady Urological Institute for permission to use the material herewith presented, also for his stimulating interest and criticism during this study, and Dr. Charles A. Waters of the Department of Roentgenology for his assistance and cooperation in taking the X-ray plates.

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PLATES

PLATE 1

Fig. 1. Cystogram taken three weeks after operation. Shows the bladder shadow round outline with margins regular. The vesical orifice is regular and shows no dilatation of the internal sphincter.

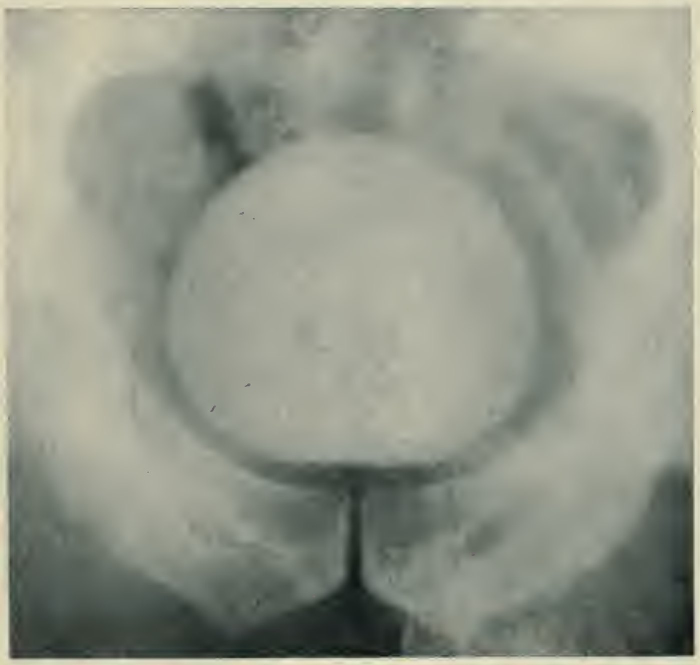

FIG. 1

PLATE 2

Fig. 2. Cystogram taken fourteen months after operation. The internal sphincter is dilated and posterior urethra is funnel-shaped as shown by the escape of the Thorium solution into the prostatic urethra. A later cystogram of this patient twenty months after operation shows the internal sphincter tightly closed, demonstrating that the internal orifice may return to normal even after a considerable interval of relaxation (see fig. 3).

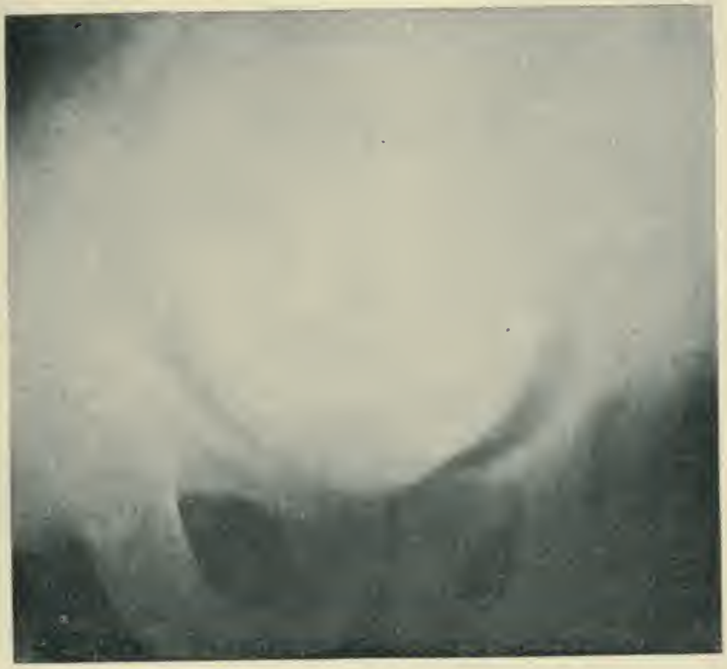

Fig. 2

PLATE 3

Fig. 3. Cystogram taken twenty months after operation. The region of the orifice is sharply delineated and shows no evidence of dilatation of the internal sphincter. In a cystogram of this patient taken fourteen months after operation the internal sphincter was found dilated (see fig. 2).

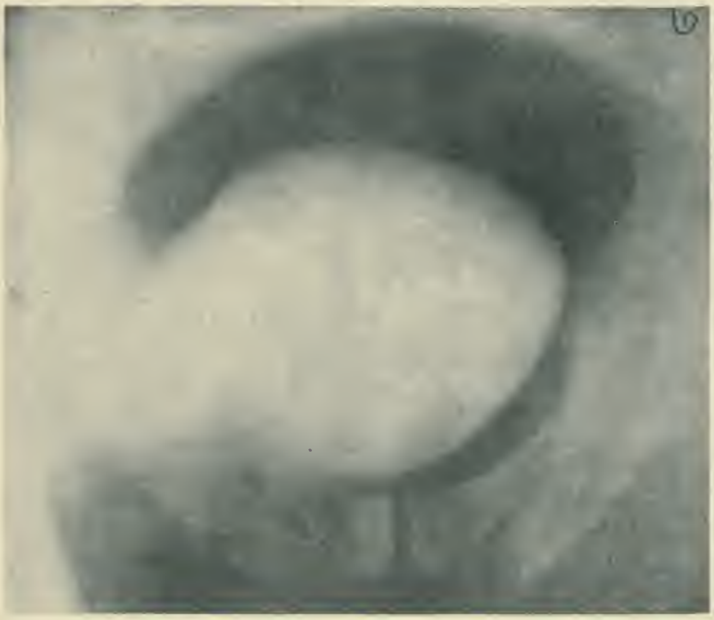

FIG. 3

A NEW METHOD FOR LOCATING SMALL CALCULI IN THE KIDNEY AT OPERATION

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Large calculi which are readily palpable through the renal cortex or renal pelvis are quite easily removed at operation, either by pyelotomy or nephrotomy, provided there be a good exposure and delivery of the kidney into the wound. In the case of small calculi it is quite difficult to locate them because they cannot be palpated and often even after the kidney is split from end to end the stone is not found because it does not lie in the line of cleavage. This splitting of the kidney is usually done near the midline and if the stone lie to either side it is often as difficult to locate it by palpation as it was before opening the kidney. The location of the stone then involves quite a great deal of mutilation of the renal parenchyma. This in itself not only causes a certain degree of irreparable damage to the renal parenchyma but necessitates the employment of numerous mattress sutures in the closure of the kidney, which in themselves are damaging to the secreting portion of the kidney tissue. Splitting the kidney also increases very markedly the possibility of post-operative hemorrhage. Probing the kidney tissue either before splitting the kidney or afterwards when it is done with no definite idea as to the location of the stone is also very damaging.

The procedure which I am about to describe has been found extremely valuable in the location of very small stones in the kidney substance. Some as small as 0.5 cm. in diameter have been located without difficulty. The requisites for success in this procedure are a good exposure of the kidney and a satisfactory delivery of it into the wound. It must be freed from the surrounding fatty capsule so that it can be easily lifted up and grasped between the thumb and fingers of the left hand. Further it is essential to have satisfactory Roentgenograms in which the outline of the kidney is clearly seen as well as the shadow of the stone. The operator must make the measurements on the kidney surface as accurate as possible so that the point at which the kidney is to be probed shall lie directly in line with the stone.

The operation for exposure of the kidney is the same as is employed in exposing the kidney for nephrectomy, nephrotomy or pyelotomy. The skin incision usually employed begins just behind the tip of the twelfth rib and extends parallel to the costal margin for a distance of 15 to 20 cm. The fascia and muscles are then divided by sharp dissection. The lumbar triangle is exposed and pierced with a blunt clamp, after which the lemon yellow fat surrounding the kidney protrudes. This opening is then enlarged and the kidney freed from its surrounding fatty capsule and delivered into the wound. In freeing the kidney great care should be exercised in ligating any adhesions which may exist between it and the surrounding tissue before dividing them because of the fact that aberrent vessels are often present at either pole of the kidney. After complete hemostasis the kidney is delivered into the wound, and its upper portion is grasped between the thumb and fingers of the left hand as shown in figure 1. The plain Roentgenogram is then examined and by means of a straight liver-needle or a fine probe the operator measures off the distance from the shadow of the stone to the border of the lower pole of the kidney (the upper pole if the stone be located in this region). The point of the needle should coincide with the center of the shadow of the stone, and the needle should be so grasped that the edge of the thumb will be on a line with the shadow of the lower border of the kidney (fig. 2). This measurement is then transferred to the surface of the kidney and the thumb of the left hand moved down to the point indicated by the end of the needle and held in this position. The same method is then employed in mapping out the distance of the stone from the convex border of the kidney, as shown in figure 3. These two points should coincide (*A* in fig. 1). Now if the liver needle be inserted perpendicular to the surface of the kidney at this point it should in its passage through the kidney come in contact with the stone. In other words, the stone lies in a line drawn perpendicular to the surface of the kidney at a point indicated by intersection of these two lines measured off on the Roentgenogram (fig. 4).

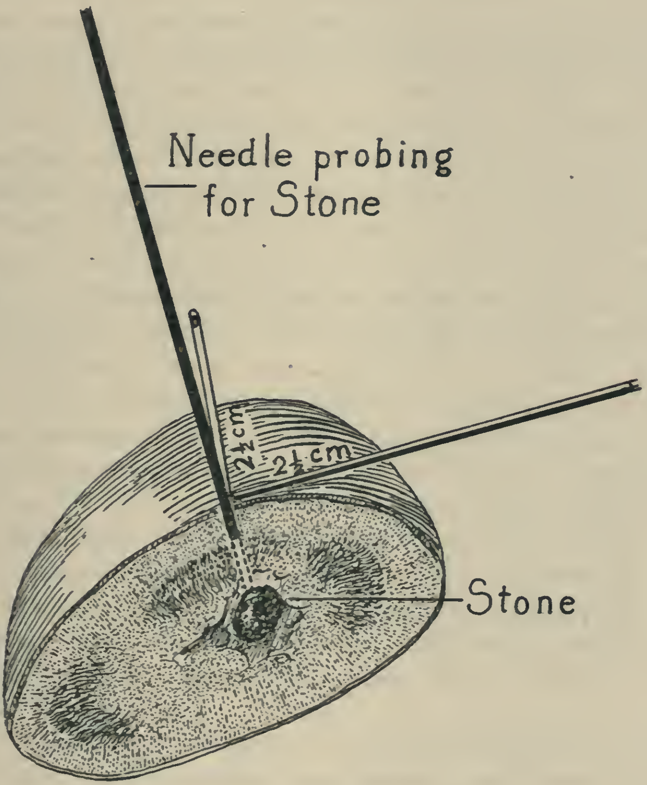


FIG. 4

After the stone has been definitely located by this means, usually by one attempt, the liver needle is withdrawn and a clamp introduced into the opening made by it, the blades separated slightly, and the stone grasped and removed. One chromic gut mattress suture is usually sufficient to close this opening. The kidney is returned to its usual position and two drains (a cigarette and a rubber tube) placed down to the opening into the kidney. The wound is then closed in the usual manner. The cigarette is removed in forty-eight hours and the tube is allowed to remain in position as long as there is any urinary drainage. It is best to suture the tube to the skin in order to be sure that its position will not be disturbed in the closure of the wound.

This method cannot be employed unless the Roentgenograms are sufficiently clear to give a good outline of the kidney as well as of the stone. It is well known that the height of the X-ray tube above the patient may cause some apparent difference in the distance of the shadow of the stone from the border of the kidney, but this has not been of sufficient degree to cause any practical difficulty in the use of the method. Another fact is that the plane of the kidney is not parallel with the surface of the X-ray plate but makes an acute angle with it. This too, has not caused any difficulty in the location of calculi by this method. The X-ray tube should be centred directly over the midline of the patient. Often the stone may lie at the extreme upper angle of a small calyx in which case its position is readily demonstrated by a pyelogram. If this be true it is often impossible to remove such a stone through the usual pyelot my incision and it can be much more readily removed by this method. Of course it must be absolutely ascertained that the calculus lies in the kidney and that the shadow on the plate is not an extrarenal shadow before any operative procedure is undertaken. This is readily done by means of pyelograms and stereoscopic plates.

Great care should be taken in making the measurements on the surface of the kidney because as is readily seen any slight deviation of the point at which the kidney surface is probed might be sufficient to cause the probe to pass to the side of a very small stone. This would usually be due to moving the kidney either from one side to the other or tilting it with the left hand while the measurements are being mapped out. If the stone should be missed on the first insertion of the probe it is not necessary to withdraw the probe entirely but only to withdraw it a short distance and change very slightly the angle of introduction.

This complication is not apt to happen if the operator is quite certain that the inserting probe is perpendicular to the surface of the kidney.

SUMMARY.

This method prevents entirely the great mutilation and destruction of kidney tissue so often seen when an ordinary nephrotomy is done and in consequence renders the operation less dangerous to the patient and a far more satisfactory procedure to the operator. The position of the stone being calculated along mathematical lines it should be located with almost absolute precision. In the four cases in which the method has been used the patient has made a prompt and uneventful recovery, and the kidney function as tested by the phthalein excretion has not been impaired.

PLATE 1

Fig. 1. Showing method of applying measurements to kidney surface for locating point (*a*) at which exploratory puncture is made.

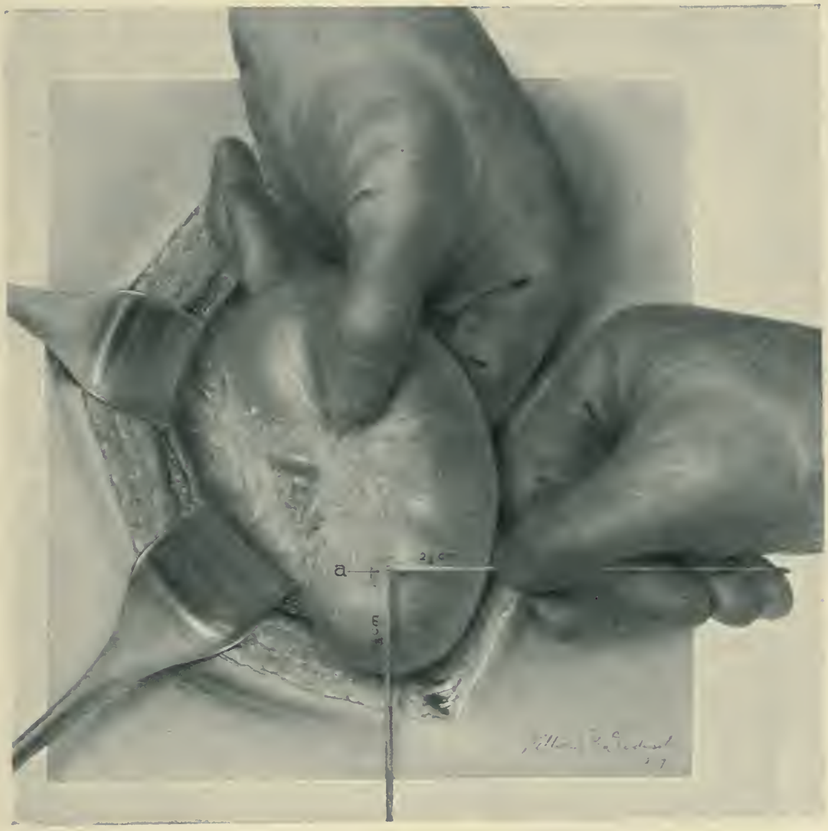

a
2½ cm
3 cm

PLATE 2

Fig. 2. Showing method of measuring distance from lower pole to shadow of stone.

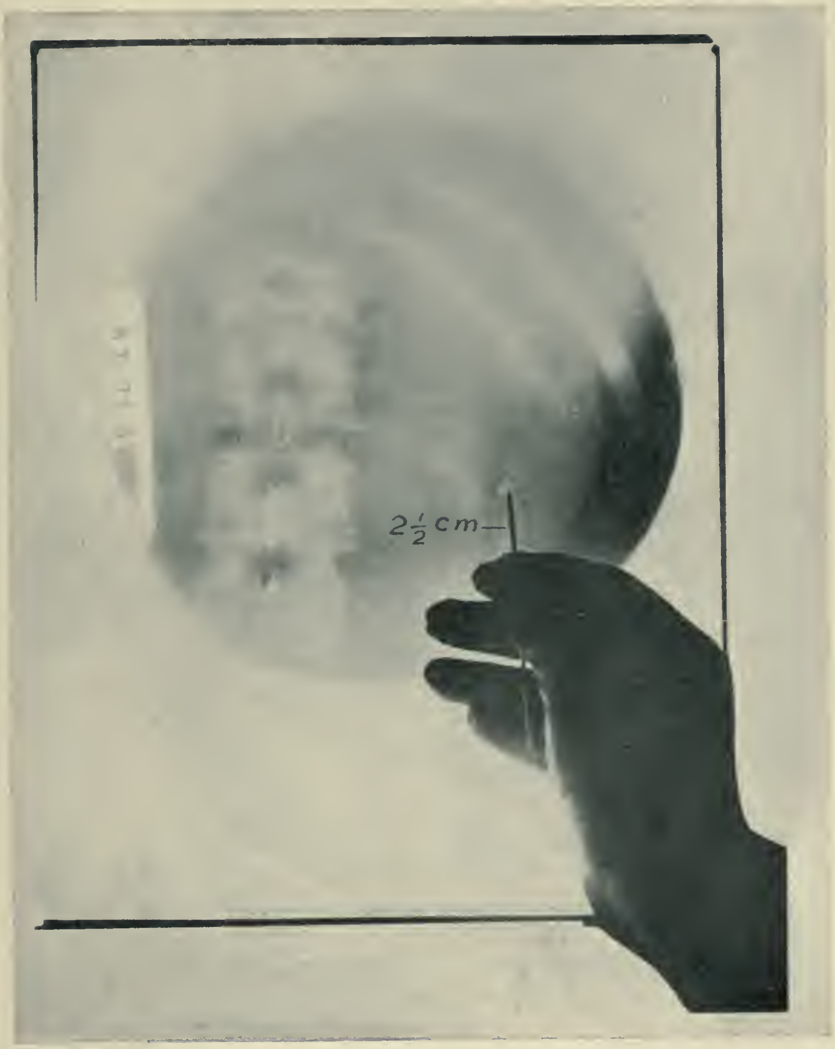
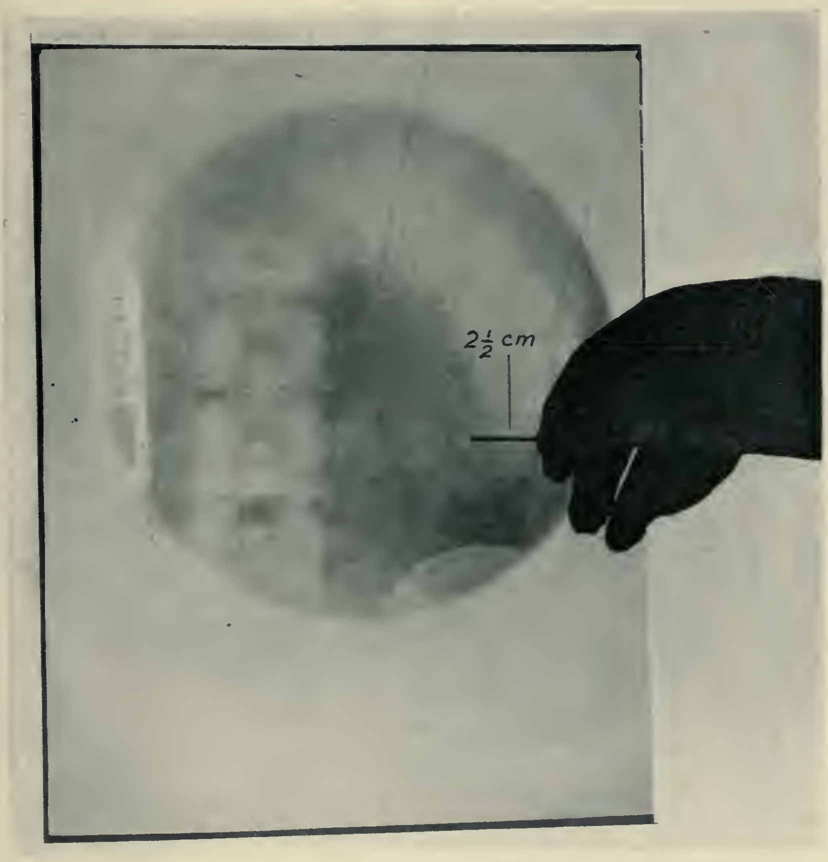

2½ cm

PLATE 3

Fig. 3. Showing method of measuring distance from convex border to shadow of stone.


$2\frac{1}{2}$ cm

A NOTE ON INJECTIONS OF PAPAVERIN IN EXPERIMENTAL SYPHILIS

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The protozoöcidal properties of emetin are well-known and have established its value as a distinct therapeutic agent in various pathological conditions more especially in the treatment of amoebic dysentery. Recent work, however, by Vedder (1), Rowntree and Levy (2), and others, has shown that this alkaloid is not devoid of toxic properties for the host, and serious poisonings have been reported following its administration. A search has therefore been made for other drugs which could take its place equally efficiently but with less danger to the patient.

Pick and Wasicky (3) noted the close chemical relationship between emetin and the opium alkaloid *papaverin* and in 1914 these authors published a comparative study of the toxicity of these two drugs for various protozoa, more especially the Paramecium, Colpidium, Amoeba, and Trypanosoma Brucei (Nagana). They found that papaverin was more toxic for Amoeba than emetin, and was surpassed in that respect only by quinin.

Macht and Fisher (4) made a further study of the subject and investigated the effect on Paramecium of all the principal alkaloids of opium. They found that the protozoöcidal properties characterized those alkaloids which belonged to the benzyl-isoquinoline group only, and on further pharmacological analysis these authors showed that the toxic part of the papaverin molecule is to be attributed to the benzyl grouping present in it.

Inasmuch as papaverin has been shown to be but little toxic for the higher animal organism and is at the same time quite toxic for protozoa in vitro, it was deemed very desirable to inquire into its possible effects on spirochaetae in the body, and accordingly the present investigation was begun. Owing to the entrance of the United States into the World War the research was not carried to the extent originally planned. Enough data were however accumulated to enable the authors to pass judgment on the effect of papaverin on experimental lues, and these are presented in the present paper.

METHOD

Two series of experiments were carried out, with three animals in each. In the first series two rabbits with fully and well-developed testicular chancres, and one rabbit with a well-developed testicular lesion produced by the spirochete of Framboesia—an organism morphologically indistinguishable from that of Syphilis—were given daily injections of a solution of papaverin hydrochloride, and the effect on the course of the lesions was noted. The injections were given intravenously and continued for three weeks, the average daily dose being about 15 mgm.

In the second series three normal rabbits were inoculated with a virulent culture of Spirochaeta pallida taken from luetic animals in the laboratory and the injections of papaverin were begun at once without waiting for the development of the luetic lesions, in order to determine whether the drug would have any prophylactic value and prevent the development of the testicular lesions ordinarily noted after inoculating with that particular strain. The dosage in this series was the same as in the first, and the injections were also continued for three weeks.

RESULTS

The prolonged and repeated injections of papaverin produced in no case any toxic symptoms of a serious nature, thus confirming the experiences on the low toxicity of the alkaloid already noted by one of the authors (5).

In the first series of experiments, no influence on the course of the disease and no effect on the lesions could be noted.

In the second series of experiments, likewise, no effect on the development of the disease or on the development of the lesions was noted. Two of the three inoculated animals developed typical testicular lesions as usual, the third was not affected. This however frequently happens.

The results of the investigation may, therefore, be briefly stated as follows: Injections of papaverin have no appreciable effect on the course of spirochaetic testicular lesions in rabbits; nor have they any influence on the development of the disease even when administered simultaneously with the inoculation of the luetic material.

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